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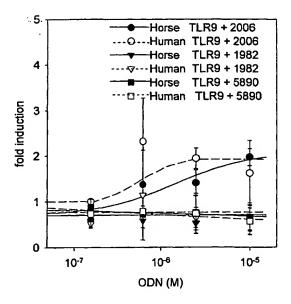
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(54) FTITIE TOLL FIRE RECEPTOR 9 (TER9) FROM-VARIOUS MAMMALIAN SPECIES



(57) Abstract: Novel amino acid and nucleotide sequences for rat, pig (porcine), cow (bovine), horse (equine), and sheep (ovine) Toll-like receptor 9 (TLR9) are provided. Also provided are amino acid and nucleotide sequences for dog (canine), cat (feline), mouse (murine), and human TLR9. Comparison of these sequences, especially in combination with functional assessment for species-specific CpG motif preferences, permits identification of specific regions and amino acid residues of interest in TLR9 ligand interaction. Novel chimeric TLR9 receptor molecules, cells expressing these molecules, and methods for their use in screening assays for TLR9 ligands are also provided.

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## TOLL-LIKE RECEPTOR 9 (TLR9) FROM VARIOUS MAMMALIAN SPECIES

## **Background of the Invention**

Synthetic oligodeoxynucleotides (ODN) and DNA containing immunostimulatory CpG motifs (CpG DNA) function as potent adjuvants and activators of the innate immune system. Heeg K et al. (2000) *Int Arch Allergy Immunol* 121:87-97; Krieg AM (2001) *Vaccine* 19:618-22. A wide variety of CpG-containing sequences have been screened for biological activity and it is reported that optimal CpG DNA sequences can vary among species. Rankin R et al. (2001) *Antisense Nucleic Acid Drug Dev* 11:333-40.

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Toll-like receptor 9 (TLR9) has recently been identified as a receptor for CpG ODN. Hemmi H et al. (2000) *Nature* 408:740-5. The molecular mechanism by which TLR9 recognizes CpG DNA is not understood.

#### Summary of the Invention

Toll-like receptor-9 (TLR9) is known to be involved in innate immunity and to signal in response to CpG DNA. To date, the amino acid sequences only of human and murine TLR9 have been reported and interestingly, these two species are known to prefer different CpG motifs. The structural basis for this species-specific CpG motif preference has not yet been fully elucidated. The instant invention provides, in part, novel amino acid and nucleotide sequences of rat, pig, cow, and horse TLR9. These novel TLR9 sequences are useful for elucidating certain key structural features of TLR9. Specifically, comparison of sequences of murine, human, and these novel TLR9 sequences permits identification of areas of highly conserved sequence, areas of group conservation, and areas of hypervariability. In addition, such comparisons permit an assessment of evolutionary relatedness among TLR9 molecules of the various species, as well as an assessment of inter-species homologies. Importantly, such comparisons permit a rational basis for identifying amino acids in TLR9 that may be involved in the CpG binding site, as well as amino acids involved in conferring species specificity for particular CpG motifs. Such information may be used to design and construct novel TLR9 molecules which incorporate specific point or regional mutations and which possess desired ligand binding characteristics. Such information may also be useful in designing and identifying novel ligands for TLR9 of a given species.

In one aspect, the invention provides isolated polypeptides having amino acid sequences for rat, pig (porcine), cow (bovine), horse (equine), and sheep (ovine) TLR9 polypeptides. These amino acid sequences correspond to SEQ ID NOs 1, 5, 9, 13, and 17, respectively. Each of these sequences is believed to include at least a majority of an extracellular domain, as well as a transmembrane region and at least part of a TLR/IL-1 receptor (TIR) domain. To the extent any such sequence may lack an amino-terminal and/or carboxy-terminal sequence, such sequence is ascertainable, without undue experimentation, using conventional molecular biology techniques and the sequence information provided herein.

In another aspect the invention provides isolated polypeptides having amino acid sequences for essentially the whole extracellular domain, optionally including a signal peptide, of each of rat, porcine, bovine, equine, and ovine TLR9. These amino acid sequences correspond to SEQ ID NOs 2, 6, 10, 14, and 18, respectively. Such extracellular domains are believed to include sequence specifically involved in binding to TLR9 ligand, such as CpG DNA. In addition, such extracellular domains are believed to include sequence that confers species specificity for particular CpG motifs.

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Isolated nucleic acid molecules encoding the polypeptides just described above are also provided according to further aspects of the invention. Such nucleic acid molecules include, but are not limited to, nucleic acid molecules having sequences provided by SEQ ID NOs 3, 7, 11, 15, 19; and 4, 8, 12, 16, and 20, respectively. Isolated nucleic acid molecules encoding the TLR9 polypeptides of SEQ ID NOs 1, 5, 9, 13, 17; and 2, 6, 10, 14, and 18 also include nucleic acid molecules that differ in sequence from SEQ ID NOs 3, 7, 11, 15, 19; and 4, 8, 12, 16, and 20, respectively, due to degeneracy of the genetic code. Such nucleic acid molecules will hybridize, under stringent conditions, with suitably selected nucleic acid molecules having sequences selected from SEQ ID NOs 3, 4, 7, 8, 11, 12, 15, 16, 19, and 20.

In another aspect the invention provides a vector which includes an isolated nucleic acid molecule of the invention. In one embodiment the vector is an expression vector and the isolated nucleic acid molecule of the invention is operably linked to a regulatory sequence in the vector. When present within a cell, an expression vector according to this aspect of the invention causes the cell to express a polypeptide of the invention.

The invention according to another aspect provides a cell in which a vector of the invention is present. In one embodiment the cell containing the vector expresses a

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polypeptide of the invention. In certain embodiments the cell also contains a reporter construct that transduces a TLR9-mediated signal in response to contact of the polypeptide of the invention or a TLR9 with a suitable TLR9 ligand. The cell containing the vector, and optionally containing the reporter construct, can be used in screening methods also provided by the invention.

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In yet another aspect the invention provides an antibody or antibody fragment that binds specifically to an isolated polypeptide of the invention. In certain embodiments the antibody or antibody fragment binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide. More specifically, the antibody or antibody fragment binds uniquely to one of the isolated polypeptides of the invention. In one embodiment the antibody or antibody fragment that binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide also binds to either mouse or human TLR9. In another embodiment the antibody or antibody fragment that binds uniquely to one of rat, porcine, bovine, equine, or ovine TLR9 polypeptide does not also bind to either mouse or human TLR9. In some embodiments 15 the antibody or antibody fragment binds selectively to a chimeric TLR9 polypeptide of the invention. In certain embodiments the antibody or antibody fragment of the invention is a monoclonal antibody or fragment of a monoclonal antibody.

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Same Comment

\*\*Invone aspects the invention provides a method for identifying key amino acids in a TER9:of affirst species which confer specificity for CpG DNA optimized for TLR9 of the 20 first-species. The method involves aligning protein sequences of TLR9 of a first species, TLR9 of a second species, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for TLR9 of the first species rather than when contacted with a CpG DNA optimized for TLR9 of the second species; generating an initial set of candidate amino acids in the TLR9 of the first species by excluding each amino acid in the TLR9 of the first species which (a) is 25 identical with the TLR9 of the second species or (b) differs from the TLR9 of the second species only by conservative amino acid substitution; generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in the TLR9 of the first species which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and 30 identifying as key amino acids in the TLR9 of the first species each amino acid in the refined set of candidate amino acids.

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In another aspect the invention provides a method for identifying key amino acids in human TLR9 which confer specificity for CpG DNA optimized for human TLR9. The method according to this aspect of the invention involves aligning protein sequences of human TLR9, murine TLR9, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for human TLR9 rather than when contacted with a CpG DNA optimized for murine TLR9; generating an initial set of candidate amino acids in human TLR9 by excluding each amino acid in human TLR9 which (a) is identical with murine TLR9 or (b) differs from murine TLR9 only by conservative amino acid substitution; generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in human TLR9 which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and identifying as key amino acids in human TLR9 each amino acid in the refined set of candidate amino acids. In one embodiment the method according to this aspect of the invention is performed iteratively with a plurality of TLR9s derived from different species other than human and mouse, wherein for each TLR9 the refined set of candidate amino acids is assigned a weight corresponding to a ratio equal to (responsiveness to human-preferred CpG DNA)/(responsiveness to murine-preferred CpG DNA).

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In another aspect the invention also provides an isolated polypeptide having an amino acid sequence identical to SEQ ID NO:30 (extracellular domain (ECD) of murine TLR9) except for substitution of at least one key amino acid identified according to the method above. The polypeptide according to this aspect of the invention is a chimeric TLR9 polypeptide. Preferably the polypeptide according to this aspect of the invention binds to CpG DNA optimized for human TLR9 better than does the isolated polypeptide having an amino acid sequence identical to SEQ ID NO:30 (ECD of murine TLR9). In one embodiment the polypeptide includes only one substituted amino acid. The isolated polypeptide according to this aspect of the invention may further include sequence involved in TLR/IL-1R signal transduction, e.g., intracellular domain of TLR9 as provided in SEQ ID NOs 29 and 33. For example, in one embodiment a polypeptide according to this aspect of the invention is an isolated polypeptide having an amino acid sequence identical to SEQ ID NO:29 (full length murine TLR9) except for substitution of at least one key amino acid identified according to the method above.

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In another aspect the invention provides an isolated nucleic acid molecule including a nucleic acid sequence encoding a chimeric TLR9 polypeptide just described. In one embodiment the isolated nucleic acid molecule has a nucleic acid sequence encoding a chimeric TLR9 polypeptide just described.

In yet another aspect, the invention provides a screening method to identify a TLR9 ligand. The method involves contacting a polypeptide (including a chimeric TLR9 polypeptide) of the invention with a candidate TLR9 ligand; measuring a signal in response to the contacting; and identifying the candidate TLR9 ligand as a TLR9 ligand when the signal in response to the contacting is consistent with TLR9 signaling. In one embodiment the candidate TLR9 ligand is an immunostimulatory nucleic acid. In one embodiment the candidate TLR9 ligand is a CpG DNA.

The invention also provides, in yet a further aspect, a screening method to identify species-specific CpG-motif preference of an isolated polypeptide of the invention. The method according to this aspect of the invention involves contacting an isolated polypeptide of the invention-with a CpG DNA including a hexamer sequence selected from the group consisting of GACGTT, AACGTT, CACGTT, TACGTT, GGCGTT, GCCGTT, GTCGTT, GATGTT, GACGTT, GA

(SEQ ID NO:39), **TCCATGACGTTTTTGATGTT TCCATAACGTTTTTGATGTT** (SEQ ID NO:40), (SEQ ID NO:41), TCCATCACGTTTTTGATGTT TCCATTACGTTTTTGATGTT (SEQ ID NO:42), 25 (SEQ ID NO:43), TCCATGGCGTTTTTGATGTT (SEQ ID NO:44), TCCATGCCGTTTTTGATGTT TCCATGTCGTTTTTTGATGTT (SEQ ID NO:45), TCCATGATGTTTTTGATGTT (SEQ ID NO:46), (SEQ ID NO:47), TCCATGAAGTTTTTGATGTT 30 TCCATGAGGTTTTTGATGTT (SEQ ID NO:48), (SEQ ID NO:49), TCCATGACATTTTTGATGTT (SEQ ID NO:50), TCCATGACCTTTTTGATGTT TCCATGACTTTTTTGATGTT (SEQ ID NO:51), (SEQ ID NO:52), TCCATGACGCTTTTGATGTT 35 TCCATGACGATTTTGATGTT (SEQ ID NO:53), TCCATGACGGTTTTGATGTT (SEQ ID NO:54),

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TCCATGACGTCTTTGATGTT (SEQ ID NO:55), TCCATGACGTATTTGATGTT (SEQ ID NO:56), and TCCATGACGTGTTTGATGTT (SEQ ID NO:57).

In certain embodiments of the screening methods of the invention, the signal includes expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway. In one embodiment the reporter gene is operatively linked to a promoter sensitive to NF-kB. In one embodiment the signal in response to contacting is binding of the candidate TLR9 ligand or CpG DNA to the polypeptide of the invention.

In one embodiment the screening method is performed on a plurality of test compounds. In one embodiment the response mediated by the TLR9 signal transduction pathway is measured quantitatively and the response mediated by the TLR9 signal transduction pathway associated with each of the plurality of test compounds is compared with a response arising as a result of an interaction between the functional TLR9 and a reference immunostimulatory compound.

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# Brief Description of the Figures

Figure 1 depicts a Clustal W multiple sequence alignment of deduced amino acid sequences for cat (feline), dog (canine), cow (bovine); mouse (murine), sheep (ovine), pig (porcine), horse (equine), human, and rat TLR9 polypeptides. The deduced amino acid sequences for feline; canine, bovine, murine, ovine, porcine, equine, human, and rat TLR9 polypeptides shown in the figure correspond to SEQ ID NOs 25, 21, 9, 29, 17, 5, 13, 33, and 1, respectively. Lines labeled "multiple" refer to the multiple sequence alignment of all six sequences shown. Lines labeled "mo/hu" refer to a paired sequence alignment of mouse and human TLR9 sequences alone.

Figure 2 is a cladogram depicting an evolutionary relatedness tree for rat, murine, porcine, bovine, equine, and human TLR9 polypeptides in Figure 1.

Figure 3 is a graph depicting species specificity of TLR9 signaling with selected oligonucleotides having strong specificity for human (2006), mouse (5890), or neither (1982).

#### **Detailed Description of the Invention**

The present invention provides novel amino acid and nucleotide sequences for TLR9 derived from rat, pig, cow, horse, and sheep. These sequences can be used to identify key features of the primary sequences of these and related TLR molecules, including previously

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known primary sequences of human and mouse (murine) TLR9. Such key features include binding site information and species specificity toward particular CpG motifs. Native and novel chimeric TLR9 polypeptides designed with the aid of this information can be expressed in vitro or in vivo and used in screening assays to identify and to design novel TLR9 ligands. Additionally, the native and novel chimeric TLR9 polypeptides designed with the aid of this information can be expressed in vitro or in vivo and used in screening assays to compare various TLR9 ligands, including CpG DNA.

In one aspect the invention provides isolated TLR9 polypeptides, and isolated nucleic acid molecules encoding them, from rat, pig, cow, horse, and sheep. The term "isolated" as used herein with reference to a nucleic acid molecule or polypeptide means substantially free of or separated from components with which it is normally associated in nature, e.g., other nucleic acids, proteins, lipids, carbohydrates or *in vivo* systems to an extent practical and appropriate for its intended use. In particular, the nucleic acids or polypeptides are sufficiently pure and are sufficiently free from other biological constituents of host cells so as to be useful in for example, producing pharmaceutical preparations. Because an isolated nucleic acid or polypeptide of the invention may be admixed with a pharmaceutically represent only a small percentage by weight of such a preparation. The nucleic acid or polypeptide is nonetheless substantially pure in that it has been substantially separated from the substances with which it may be associated in living systems.

An amino acid sequence of rat TLR9 is provided as SEQ ID NO:1. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:1 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of rat TLR9 (See Figure 1). Amino acids numbered 1-821 of SEQ ID NO:1 are presumptively extracellular domain and correspond to SEQ ID NO:2. SEQ ID NO:3 is a nucleotide sequence of rat TLR9 cDNA having an open reading frame corresponding to nucleotides 1-3096. SEQ ID NO:4 is a nucleotide sequence of rat cDNA encoding amino acids 1-821 of SEQ ID NO:1.

An amino acid sequence of porcine TLR9 is provided as SEQ ID NO:5. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:5 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of porcine TLR9

(See Figure 1). Amino acids numbered 1-819 of SEQ ID NO:5 are presumptively extracellular domain and correspond to SEQ ID NO:6. SEQ ID NO:7 is a nucleotide sequence of porcine TLR9 cDNA having an open reading frame corresponding to nucleotides 77-3166. SEQ ID NO:8 is a nucleotide sequence of porcine cDNA encoding amino acids 1-819 of SEQ ID NO:5.

An amino acid sequence of bovine TLR9 is provided as SEQ ID NO:9. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:9 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of bovine TLR9 (See Figure 1). Amino acids numbered 1-818 of SEQ ID NO:9 are presumptively extracellular domain and correspond to SEQ ID NO:10. SEQ ID NO:11 is a nucleotide sequence of bovine TLR9 cDNA having an open reading frame corresponding to nucleotides 84-3170. SEQ ID NO:12 is a nucleotide sequence of bovine cDNA encoding amino acids 1-818 of SEQ ID NO:9.

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An amino acid sequence of equine TLR9 is provided as SEQ ID NO:13. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:13 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of equine TLR9 (See Figure 1). Amino acids numbered 1-820 of SEQ ID NO:13 are presumptively extracellular domain and correspond to SEQ ID NO:14. SEQ ID NO:15 is a nucleotide sequence of equine TLR9 cDNA having an open reading frame corresponding to nucleotides 115-3207. SEQ ID NO:16 is a nucleotide sequence of equine cDNA encoding amino acids 1-820 of SEQ ID NO:13.

An amino acid sequence of ovine TLR9 is provided as SEQ ID NO:17. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:17 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of ovine TLR9 (See Figure 1). Amino acids numbered 1-818 of SEQ ID NO:17 are presumptively extracellular domain and correspond to SEQ ID NO:18. SEQ ID NO:19 is a nucleotide sequence of ovine TLR9 cDNA having an open reading frame corresponding to nucleotides 92-3178. SEQ ID NO:20 is a nucleotide sequence of ovine cDNA encoding amino acids 1-818 of SEQ ID NO:17.

### SEQ ID NO:1 (Rat TLR9)

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MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAEPRSNITSLSLIANRI
HHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFLAMRMLEELNLSYNGITTVPRLPSSLTNLSL
SHTNILVLDASSLAGLHSLRVLFMDGNCYYKNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYL
LLSYNLIVKLGAEDLANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN
SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSFKSLVSLQELNMNGIF
FRILNKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFVDLSNNRISGPPTLSRVAPEKADEAEKGVPW
PASLTPALPSTPVSKNFMVRCKNLRFTMDLSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLK
VLDLSYNKLDLYHSKSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSTS
VEYLDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKLSFRDNHLSFFNWSSLA
FLPNLRDLDLAGNLLKALTNGTLPNGTLLQKLDVSSNSIVFVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
MNLTVLDVSSNPLHCACGAPFVDLLLEVQTKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFGLSLL
AVAVGTVLPLLQHLCGWDVWYCFHLCLAWLPLLTRGRRSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEERRG
RRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDKVSGLLRTSFLLAQQRLLEDRKDVVVLVILRPDA
HRSRYVRLRORLCROSVLFWPHOPNGQGSFWAQLSTALTRDNHHFYNRNFCRGPTAE

## SEQ ID NO:2 (Rat TLR9)

MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAEPRSNITSLSLIANRI
HHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFLAMRMLEELNLSYNGITTVPRLPSSLTNLSL
SHTNILVLDASSLAGLHSLRVLFMDGNCYYKNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPRQLPPSLEYL
LLSYNLIVKLGAEDLANLTSLRMLDVGGNCRRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN
SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSFKSLVSLQELNMNGIF
FRILINKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFVDLSNNRISGPPTLSRVAPEKADEAEKGVPW

25 \*PASLTPALPSTPVSKNFMVRCKNLRFTMDLSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLK
VLDLSYNKLDLYHSKSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSTS
\*VEYIDFSGNGVGRMWDEEDLYLYFFQDLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKLSFRDNHLSFFNWSSLA
\*FLENERDLDLAGNLLKATTNGTLPNGTLLQKLDVSSNSLVFVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV
\*\*MNLTWLDVSSNPLHCAGGAPFVDLLLEVQTKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFG

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Land Bridge Contract

#### SEQ ID NO:3 (Rat TLR9)

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## SEQ ID NO:4 (Rat TLR9)

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atggttetetgtegeaggaccetgeacceettgtetetetetggtacaggeegeagtgetggetgaggetetggee ctgggtaccctgccttcctaccctgtgaactgaagcctcatggcctggtagactgcaactggctcttcctg 25 aagtetgtgeeteaettetetgeegeagaaeeeegtteeaaeateaeeageettteettgategeeaaeegeate  $\tt caccacctgcacacctcgactttgtccacctgcccaacgttgcgacagctgaacctcaagttggaactgtccgccc$ cetggceteageccettgcacttetcctgccgcatgaccattgagcccaaaaccttcctggctatgcgcatgctg gaagagetgaacetgagetataaeggtateaceaetgtgeeeeggeetgeeeageteeetgaegaatetgageeta agccacaceaacatcctggtactcgatgccageagcctcgctggcctgcacagcctgcgägttctcttcatggac 30 gggaactgctactacaagaacccctgcaacggggcggtgaacgtgaccccggacgccttcctgggcttgagcaac ctcaccacttgtcccttaagtataacaacctcacagaggtgccccgccaactgccccccagcctggagtacctc ctgctgtcctataacctcatcgtcaagctgggggccgaagacctagccaacctgacctcccttcgaatgcttgat gtgggtgggaattgccgtcgctgtgatcacgcccccgacctctgtacagaatgccggcagaagtcccttgatctg caccetcagactttccatcacctgagccaccttgaaggcctggtgctgaaggacagttctctccactcgctgaac 35 tccaagtggttccagggtctggcgaacctctcggtgctggacctaagcgagaactttctctacgagagcatcaac aaaaccagcgcctttcagaacctgacccgtctgcgcaagctcgacctgtccttcaattactgcaagaaggtatcg ttcgcccgcctccacctggcaagttccttcaagagcctggtgtcgctgcaggagctgaacatgaacggcatcttc aatttcatcaaccaggcgcagctcagcgtctttagtaccttccgagcccttcgctttgtggacctgtccaataat 40 cgcatcagcgggcctccaacgctgtccagagtcgccccgaaaaaggcagacgaggcggagaagggggttccatgg cctgcaagtctcacccagctctcccgagcactcccgtctcaaagaacttcatggtcaggtgtaagaacctcaga ttcaccatggacctgtctcggaacaaccaggtgactatcaagccagagatgttcgtcaacctctcccatctccag tgtctgagcctgagccacaactgcatcgcgcaggctgtcaatggctctcagttcctgccgctgaccaacctgaag gtgctggacctgtcctataacaagctggacctgtaccattcgaaatcgttcagtgagctcccacagttgcaggcc 45 ctggacctgagctacaacagccagccattcagcatgcaggggataggccacaacttcagttttctggccaatctg tccaggttacagaaccttagcctggcacacaatgacattcacagccgcgtgtcctcacgcctctacagcacctca gtggagtatctggacttcagcggcaacggtgtggggccgcatgtgggacgaggaggacctttacctctatttcttc caagacctgagaagcctgattcatctggacctgtctcagaataagctgcacatcctccggccccagaacctcaac tacetccccaagagcetgacgaagctgagtttccgtgacaatcacctctetttetttaactggagcagtetggcc 50 ttcctgcccaatctgcgagacctggacctggcaggcaatctactaaaaggccctgaccaacggcaccctgcctaat ggcacgctcctccagaaactggatgtcagtagcaacagtatcgtctttgtggtcccagccttctttgctctggcg gtagagetaaaagaggteaaceteageeataacateeteaagactgtggategeteetggtttgggeeeattgtg atgaacctgacggttctagacgtgagcagcaaccctctgcattgtgcctgcggtgcaccctttgtagacttactg ctggaagtgcagaccaaggtgcctggcctggctaacggtgtgaagtgtggcagtccccgccagctgcaggccgc 55 agcatetttgegeaagaeetgeggetgtgeetggatgaegteetttetegggaetgetttgge

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#### SEQ ID NO:5 (Porcine TLR9)

MGPRCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRANVTSLSLLSNRIH HLHDSDFVHLSSLRTLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNSITTVPALPDSLVSLSLS RTNILVLDPTHLTGLHALRYLYMDGNCYYKNPCOGALEVVPGALLGLGNLTHLSLKYNNLTEVPRSLPPSLETLL 5 LSYNHIVTLTPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLDT RWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSFGHLRSLKELDMHGIFF  ${\tt RSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYVDLSDNRISGAARPVAITREVDGRERVWLPSR}$ NLAPRPLDTLRSEDFMPNCKAFSFTLDLSRNNLVTIQSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVL DLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASLC ALDFSGNDLSRMWAEGDLYLRFFQGLRSLVWLDLSQNHLHTLLPRALDNLPKSLKHLHLRDNNLAFFNWSSLTLL 10 PKLETLDLAGNQLKALSNGSLPSGTQLRRLDLSGNSIGFVNPGFFALAKQLEELNLSANALKTVEPSWFGSMVGN LKVLDVSANPLHCACGATFVGFLLEVQAAVPGLPSRVKCGSPGQLQGHSIFAQDLRLCLDETLSWNCFGISLLAM ALGLVVPMLHHLCGWDLWYCFHLCLAWLPHRGQRRGADALFYDAFVVFDKAQSAVADWVYNELRVQLEERRGRRA  $\verb|LRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPDAYRS|$ 15 RYVRLRORLCROSVLLWPHOPRGQGSFWAQLGTALTRDNHHFYNRNFCRGPTTAE

## SEQ ID NO:6 (Porcine TLR9)

MGPRCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRANVTSLSLLSNRIH
HLHDSDFVHLSSLRTLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNSITTVPALPDSLVSLSLS

RTNILVLDPTHLTGLHALRYLYMDGNCYYKNPCQGALEVVPGALLGLGNLTHLSLKYNNLTEVPRSLPPSLETLL
LSYNHIVTLTPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLDT
RWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSFGHLRSLKELDMHGIFF
RSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYVDLSDNRISGAARPVAITREVDGRERVWLPSR
NLAPRPLDTLRSEDFMPNCKAFSFTLDLSRNNLVTIQSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVL
DESHNKLDLYHGRSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASLC
ALDFSGNDLSRMWAEGDLYLRFFQGLRSLVWLDLSQNHLHTLLPRALDNLPKSLKHLHLRDNNLAFFNWSSLTLL
PKLETLDLAGNQLKALSNGSLPSGTQLRRLDLSGNSIGFVNPGFFALAKQLEELNLSANALKTVEPSWFGSMVGN

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#### 30 SEQ ID NO 7 (Porcine TLR9)

gggcaggctgcctgccttcctgccctgtgagctccagcccacggcctggtgaactgcaactggctcttcctgaa gtccgtgccccaettctcggcggcagcgccccgggccaacgtcaccagcctctccttactctaaccgcatcca ccacctgcacgactccgacttcgtccacctgtccagcctacgaactctcaaacctcaagtggaactgcccgccggc tggcctcagccccatgcacttcccctgccacatgaccatcgagcccaacaccttcctggccgtgcccaccctgga caactgctactactacaagaacccctgccagggggcgctggaggtggtgccgggtgccctcctcggcctgggcaacct 40 cacacatctctcactcaagtacaacatctcacggaggtgccccgcagcctgcccccagcctggagaccctgct gttgtcctacaaccacattgtcaccctgacgcctgaggacctggccaatctgactgccctgcgcgtgcttgatgt gggggggaactgccgccgctgtgaccatgcccgcaacccctgcagggagtgcccaaaggaccaccccaagctgca ctctgacaccttcagccacctgagccgcctcgaaggcctggtgttgaaagacagttctctctacaacctggacac 45 gaccacggccttccagggcctggcccgactgcgcagcctcaacctgtccttcaattaccacaagaaggtgtcctt ccgctcgctcagtgagaccacgctccaacctctggtccaactgcctatgctccagaccctgcgcctgcagatgaa cttcattaaccaggcccagctcagcatcttttggggccttccctggcctgctgtacgtggacctatcggacaaccg catcagcggagctgcaaggccagtggccattactagggaggtggatggtagggagagggtctggcttccag 50 gaacctcgctccacgtccactggacactctccgctcagaggacttcatgccaaactgcaaggccttcagcttcac cttggacctgtctcggaacaacctggtgacaatccagtcggagatgtttgctcgcctctcacgcctcgagtgcct gcgcctgagccacaacagcatctcccaggcggtcaatggctctcagtttgtgccgctgaccagcctgcgggtgct ggacctgtcccacaacaagctggacctgtatcacgggcgctcgttcacggagctgccggcctggaagcactgga cctcagctacaatagccagccctttaccatgcagggtgtgggccacaacctcagcttcgtggcccagctgcccgc

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### SEQ ID NO:8 (Porcine TLR9)

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25 ggcaggctgcctgccttcctgccctgtgagctccagccccacggcctggtgaactgcaactggctcttcctgaaq teegtgeeceaetteteggeggeagegeeegggeeaacgteaceageeteteettactetecaacegeateeae cacetgeacgaeteegaettegteeacetgteeageetaegaacteteaaceteaagtggaactgeeegeegget ggcctcagccccatgcacttcccctgccacatgaccatcgagcccaacacttcctggccgtgcccaccctggag 30 acacateteteaeteaagtacaacaateteaeggaggtgeeeegeageetgeeeecageetggagaeeetgetg ttgtcctacaaccacattgtcaccctgacgcctgaggacctggccaatctgactgccctgcgcgtgcttgatgtg ggggggaactgccgccgctgtgaccatgcccgcaacccctgcagggagtgcccaaaqqaccaccccaaqctqcac tetgacacettcagecacetgageegeetegaaggeetggtgttgaaagacagttetetetacaacetggacace  ${\tt accacggccttccagggcctggcccgactgcgcagcctcaacctgtccttcaattaccacaagaaggtgtccttt}$  ${\tt gcccacctgcacctgggcacctcctftgggcacctccggtccctgaaggagctggacatgcatggcatcttcttc}$  $\verb|cgctcgctcagtgagaccacgctccaacctctggtccaactgcctatgctccagaccctgcgcctgcagatgaac| \\$ 40 ttcattaaccaggcccagctcagcatctttggggccttccctggcctgctgtacgtggacctatcggacaaccgc atcagcggagctgcaaggccagtggccattactagggaggtggatggtagggagaggggtctggcttccagg  ${\tt aacctcgctccacgtccactggacactctccgctcagaggacttcatgccaaactgcaaggccttcagcttcacc}$  $\verb|ttggacctgtctcggaaccaacctggtgaccaatccagtcggagatgtttgctcgcctctcacgcctcgagtgcctg|$  $\verb|cgcctgagccacaacagcatctcccaggcggtcaatggctctcagtttgtgccgctgaccagcctgcgggtgctg|$ 45 gacetgteccacaacaagetggacetgtateaegggegetegtteaeggagetgeegeceggcaetggaageaetggae  $\verb|ctcagctacaatagccagccctttaccatgcagggtgtgggccacaacctcagcttcgtggcccagctgcccgcc|$ ctgcgctacctcagcctggcgcacaatgacatccatagccgagtgtcccagcagctctgtagcgcctcactgtgc gccctggactttagcggcaacgatctgagccggatgtgggctgagggagacctctatctccgcttcttccaaggc  $\verb|ctaagaagcctagtctggacctgtcccagaaccacctgcacacctcctgccacgtgccctggacaacctc|$ 50 cccaaaagcctgaagcatctgcatctccgtgacaataacctggccttcttcaactggagcagcctgaccctcctg  $\verb|ccc|| aagetggaaaccetggaattggetggaaaccagetgaaggeectaageaattggeageetgeeatetggeacc||$ cagctgcggaggctggacctcagtggcaacagcatcggctttgtgaaccctggcttctttgccctggccaagcag ttagaagagctcaacctcagcgccaatgccctcaagacagtggagccctcctggtttggctcgatggtgggcaac ctgaaagtcctagacgtgagcgccaaccctctgcactgtgcctgtggggcgaccttcgtgggcttcctgctggag 55 gtacaggetgccgtgcctgggctgcccagccgcgtcaagtgtggcagtccggggcagctccagggccatagcatc tttgcgcaagacctgcgcctctgcctggatgagaccctctcgtggaactgttttggc

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#### SEQ ID NO:9 (Bovine TLR9)

MGPYCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGAPRANVTSLSLISNRIH HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS HTSILVLGPTHFTGLHALRFLYMDGNCYYMNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL LSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK DWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSFGSLVSLEKLDMHGIFF RSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFVDLSDNRISGAATPAAALGEVDSRVEVWRLPR GLAPGPLDAVSSKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLD 10 LSHNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSENHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP RLEALDLAGNQLKALSNGSLPPGIRLQKLDVSSNSIGFVIPGFFVRATRLIELNLSANALKTVDPSWFGSLAGTL KILDVSANPLHCACGAAFVDFLLERQEAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFGLSLLMVA LGLAVPMLHHLCGWDLWYCFHLCLAHLPRRRRQRGEDTLLYDAVVVFDKVQSAVADWVYNELRVQLEERRGRRAL 15 RLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPAAYRSR YVRLRQRLCRQSVLLWPHQPSGQGSFWANLGIALTRDNRHFYNRNFCRGPTTAE

## SEQ ID NO:10 (Bovine TLR9)

MGPYCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGAPRANVTSLSLISNRIH

20 HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS
HTSILVLGPTHFTGLHALRFLYMDGNCYYMNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL
LSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK
DWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSFGSLVSLEKLDMHGIFF
RSETNITLQSLTRLPKLQSLHLQLNFINQAQLSTFGAFPSLLFVDLSDNRISGAATPAAALGEVDSRVEVWRLPR

25 GLAPGPLDAVSSKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLD
LSHNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA
LIDFSGNSUSQMWAEGDLYLGFFKGLRNLVQLDESENHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP
"REEALDLAGNQLKALSNGSUPPGIRLQKLDVSSNSTGFVIPGFFVRATRLIELNLSANALKTVDPSWFGSLAGTL
KILDVSANPLHCACGAAFVDFLLERQEAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFG

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TO THE WAR PARTY

SEQ ID NO:11 (Bovine TLR9)

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gggaagtgggcgccaagcatccttccctgcagctgcctcccaacctgcccgccagaccctctggagaagccgcat tecetgteatgggeceetactgtgeceegeacceetttetetetetggtgeaggeggeggeaetggeageggeee tggccgagggcaccctgccttcctgccctgtgagctccagccccatggtcaggtggactgcaactggctgt teetgaagtetgtgeegeaetttteggetggageeeeeegggeeaatgteaeeageeteteettaateteeaaee geatecaccacttgeatgactetgacttegtecacctgtecaacctgegggtecteaaccteaagtggaactgee egeeggeeggeeteageeeeatgeactteecetgeegtatgaceategageeeaacacetteetggetgtgeeea 40 tggacggcaactgctactacatgaacccctgcccgcgggccctggaggtggccccaggcgccctcctcggcctgg gcaacctcacgcacctgtcgctcaagtacaacatctcacggaggtgccccgccgcctgcccccagcctggaca ccctgctgctgtcctacaaccacattgtcaccctggcacccgaggacctggccaacctgactgccctgcgcgtgc ttgacgtgggtgggaactgccgccgctgcgaccatgcccgcaacccctgcagggagtgcccaaagaacttcccca agctgcaccctgacaccttcagtcacctgagccgcctcgaaggcctggtgttgaaggacagttctctctacaaac 45 tcaccaagaccaccatcttcaacgacctgacccagctgcgcagactcaacctgtccttcaattaccacaagaagg tgtccttcgcccacctgcacctagcgtcctcctttgggagtctggtgtccctggagaagctggacatgcacggca tettetteegeteeeteaceaacateaegeteeagtegetgaceeggetgeeeaageteeagagtetgeatetge agctgaacttcatcaaccaggcccagctcagcatctttggggccttcccgagcctgctcttcgtggacctgtcgg 50 acaaccgcatcagcggagccgcgacgccagcggccgccctgggggaggtggacagcagggtggaagtctggcgat tgcccaggggcctcgctccaggcccgctggacgccgtcagctcaaaggacttcatgccaagctgcaacctcaact tcaccttggacctgtcacggaacaacctggtgacaatccagcaagagatgtttacccgcctctcccgcctccagt gcctgcgcctgagccacaacagcatctcgcaggcqqttaatqqctcccaqttcqtgccgctgaccaqcctgcgaq

tgctcgacctgtcccacaacaagctggacctgtaccatgggcgctcattcacggagctgccgcagctggaggcac tggaceteagetacaacagecageeetteageatgeagggegtgggecacaaeeteagettegtggeeeagetge cctccctgcgctacctcagccttgcgcacaatggcatccacagccgcgtgtcacagaagctcagcagcgcctcgt tgcgcgccctggacttcagcggcaactccctgagccagatgtgggccgaggggagacctctatctctgctttttca aaggottgaggaacetggtccagetggacetgtccgagaaccatetgcacaccetcctgcctcgtcacctggaca acetgeecaagageetgeggeagetgegteteegggaeaataacetggeettetteaactggageageetgaeeg teetgeeeeggetggaageeetggatetggeaggaaaceagetgaaggeeetgageaacggeageetgeegeetg gcatccggctccagaagctggacgtgagcagcaacagcatcggcttcgtgatccccggcttcttcgtccgcgcga ctcggctgatagagcttaacctcagcgccaatgccctgaagacagtggatccctcctggttcggttccttagcag 10 tggagagacaggaggccgtgcccgggctgtccaggcgcgtcacatgtggcagtccgggccagctccagggccgca gcatcttcacacaggacctgcgcctctgcctggatgagaccctctccttggactgctttggcctctcactgctaa tggtggcgctgggcctggcagtgcccatgctgcaccacctctgtggctgggacctctggtactgcttccacctgt gtctggcccatttgccccgacggcggcggcggggggggaggacaccctgctctatgatgccgtcgtggtcttcg 15 acaaggtgcagagtgcagtggctgattgggtgtacaacgagctccgcgtgcagctggaggagcgccggggggcgcc gggcgctccgcctctgcctggaggagcgagactggctccctggtaagacgctcttcgagaacctgtgggcctcgg tctacagcagccgcaagaccatgttcgtgctggaccacacggaccgggtcagcggcctcctgcgcgccagcttcc tgctggcccagcagcgcctgttggaggaccgcaaggacgtcgtagtgctggtgatcctgcgccccgccgcctatc ggtcccgctacgtgcggctgcgccagcgcctctgccgccagagcgtcctcctcttggccccaccagcccagtggcc 20  ${\tt agggtagtttetgggccaacctgggcatagccctgaccagggacaaccgtcacttctataaccggaacttctgcc}$ ggggccccacgacagccgaatagcacagagtgactgcccag

#### SEQ ID NO:12 (Bovine TLR9)

atgggcccctactgtgccccgcaccccctttctctctctggtgcaggcggcactggcagcggccctggccgag 25 ggcaccctgcctgccttcctgccctgtgagctccagccccatggtcaggtggactgcaactggctgttcctgaag tetgtgcegcaetttteggetggageceeegggecaatgteaccagecteteettaatetecaacegcatecae cacttgcatgactctgacttcgtccacctgtccaacctgcgggtcctcaacctcaagtggaactgcccgccgcc ggeeteagecceatgeactteccetgeegtatgaecategageedaacacettectggetgtgeecaceetggag gagetgaacetgagetàcaacggeatcacgaecgtgecetgecetgecagttecetegtgtecetgtegetgage 30 cacaccageatectggtgctaggccccacccacttcaccggcctgcacgccctgcgctttctgtacatggacggc aactgctactacatgaacccctgcccgoggccctggaggtggccccaggcgccctcctcggcctgggcaacctc acgcacctgtcgctcaagtacaacaacctcacggaggtgccccgccgcctgccccccagcctggacaccctgctg ctgtcctacaaccacattgtcaccctggcacccgaggacctggccaacctgactgccctgcgcgtgcttgacgtg ggtgggaactgccgccgctgcgaccatgcccgcaacccctgcagggagtgcccaaagaacttccccaagctgcac 35 cctgacaccttcagtcacctgagccgcctcgaaggcctggtgttgaaggacagttctctctacaaactagagaaa accaccatetteaacgacetgacecagetgegeagacteaacetgteetteaattaceacaagaaggtgteette gcccacctgcacctagcgtcctcctttgggagtctggtgtccctggagaagctggacatgcacggcatcttcttc cgctccctcaccaacatcacgctccagtcgctgacccggctgcccaagctccagagtctgcatctgcagctgaac 40 tteateaaccaggcccagctcagcatetttggggccttcccgagcctgctcttcgtggacctgtcggacaaccgc atcageggageegegaegeeageggeegeetggggggggtggaeageagggtggaagtetggegattgeeeagg ggcctcgctccaggcccgctggacgccgtcagctcaaaggacttcatgccaagctgcaacctcaacttcaccttg gacctgtcacggaacaacctggtgacaatccagcaagagatgtttacccgcctctcccgcctccagtgcctgcgc ctgagccacaacagcatctcgcaggcggttaatggctcccagttcgtgccgctgaccagcctgcgagtgctcgac ctgtcccacaacaagctggacctgtaccatgggcgctcattcacggagctgccgcagctggaggcactggacctc cgctacctcagccttgcgcacaatggcatccacagccgcgtgtcacagaagctcagcagcgcctcgttgcgcgcc ctggacttcagcggcaactccctgagccagatgtgggccgagggagacctctatctctgctttttcaaaggcttg aggaacctggtccagctggacctgtccgagaaccatctgcacaccctcctgcctcgtcacctggacaacctgccc  ${\tt aagagcctgcggcagctgcgtctccgggacaataacctggccttcttcaactggagcagcctgaccgtcctgccc}$ cggctggaagccctggatctggcaggaaaccagctgaaggccctgagcaacggcagcctgccgcctggcatccgg ctccagaagctggacgtgagcagcaacagcatcggcttcgtgatccccggcttcttcgtccgcgcgactcggctg aaaatcctagacgtgagcgccaacccgctccactgcgcctgcggggcggcctttgtggacttcctgctggagaga 55 caggaggccgtgcccgggctgtccaggcgcgtcacatgtggcagtccgggccagctccagggccgcagcatcttc acacaggacctgccctctgcctggatgagaccctctccttggactgctttggc

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## SEQ ID NO:13 (Equine TLR9)

 ${\tt MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRDNVTSLSLLSNRI}$ HHLHDSDFAQLSNLQKLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLIL SRTNILOLDPTSLTGLHALRFLYMDGNCYYKNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYL  $\verb|LLSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCVECPHKFPQLHSDTFSHLSRLEGLVLKDSSLYOLN|$ PRWFRGLGNLTVLDLSENFLYDCITKTKAFQGLAQLRRLNLSFNYHKKVSFAHLTLAPSFGSLLSLQELDMHGIF  ${\tt FRSLSQKTLQPLARLPMLQRLYLQMNFINQAQLGIFKDFPGLRYIDLSDNRISGAVEPVATTGEVDGGKKVWLTS}$  ${\tt RDLTPGPLDTPSSEDFMPSCKNLSFTLDLSRNNLVTVQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQV}$ LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSTSL 10 WALDFSGNSLSQMWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLLRLRNNYLAFFNWSSLTL  $\verb|LPNLETLDLAGNQLKALSNGSLPSGTQLQRLDVSRNSIIFVVPGFFALATRLRELNLSANALRTEEPSWFGFLAG|$  ${\tt SLEVLDVSANPLHCACGAAFVDFLLQVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFGLSLLV}$ VALGLAMPMLHHLCGWDLWYCFHLGLAWLPRRGWQRGADALSYDAFVVFDKAQSAVADWVYNELRVRLEERRGRR ALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRLLEDRKDVVVLVILSPDARR 15  ${\tt SRYVRLRQRLCRQSVLFWPHQPSGQRSFWAQLGMALTRDNRHFYNQNFCRGPTMAE}$ 

#### SEQ ID NO:14 (Equine TLR9)

MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAAPRDNVTSLSLLSNRI
HHLHDSDFAQLSNLQKLNLKWNCPPAGLSPMHFPCHMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLIL
SRTNILQLDPTSLTGLHALRFLYMDGNCYYKNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYL
LLSYNHIVTLAPEDLANLTALRVLDVGGNCRRCDHARNPCVECPHKFPQLHSDTFSHLSRLEGLVLKDSSLYQLN
PRWFRGLGNLTVLDLSENFLYDCITKTKAFQGLAQLRRLNLSFNYHKKVSFAHLTLAPSFGSLLSLQBLDMHGIF
FRSLSQKTLQPLARLPMLQRLYLQMNFINQAQLGIFKDFPGLRYIDLSDNRISGAVEPVATTGEVDGGKKVWLTS
RDLTPGPLDTPSSEDFMPSCKNLSFTLDLSRNNLVTVQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQV
LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSTSI
WALDFSGNSLSQMWAEGDLYERFFQGERSLEREDLSQNRLHTLLPCTLGNLPKSLQLLRLRNNYLAFFNWSSLTL
LPNLETLDLAGNQLKALSNGSLPSGTQLQRLDVSRNSITFVVPGFFALATRLRELNLSANALRTEEPSWFGFLAG
SLEVLDVSANPLHCACGAAFVDFLLQVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFG

 $\dots, \dots, n_{i_1, \dots}$ 

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#### SEO ID NO:15 (Equine TLR9)

 $\verb|ctctgttctctgagctgttgccgcgtgaagggactgcgagcacaaagcatcctcttgcagctgctgcccagtg|$ tqccaqctggaccctctggatcatctcccactccctgtcatgggcccttgccatggtgccctgcagcccctgtct ctcctqqtgcaggcggccatgctggccgtggctctggcccaaggcaccctgcctcccttcctgccctgtgagctc cagccccacggcctggtgaactgcaactggctgttcctgaagtccgtgccccacttctcagcagcaccccgg 35 gacaatgtcaccagcctttccttgctctccaaccgcatccaccacctccacgactccgactttgcccaactgtcc aacctgcagaaactcaacctcaaatggaactgcccgccagccggcctcagccccatgcacttcccctgccacatg accatcqaqcccaacactttcctqqctqtacccaccctqqaqgaqctgaacctgagctacaacggcatcacgact qtqcctqccctqcccaqctccctcgtqtccctgatcctgagccgcaccaacatcctgcagctagaccccaccagc 40 ctgqaqqtgqccccaggcgccctccttggcctgggcaacctcacccacctgtcactcaagtacaaccacctcaca acqqtqccccqcagcctgccccctagcctggagtacctgctgttgtcctacaaccacattgtcaccctggcacct qaqqacctqqccaatctgactqccctqcqtqtqctcqatqtgggtqgaaactqccgccgctgtgaccatqcacqc aacccctgcgtggagtgcccacataaattcccccagctgcactccgacaccttcagccacctaagccgcctagaa 45 qqcctcqtqttqaaqqataqttctctctaccaqctqaaccccaqatqgttccgtggcctgggcaacctcacagtg ctcgacctgagtgagaacttcctctacgactgcatcaccaaaaccaaggcattccagggcctggcccagctgcga agactcaacttgtccttcaattaccataagaaggtgtccttcgcccacctgacgctggcaccctccttcgggagc gecegeetgeecatgeteeagegtetgtatetgeagatgaaetteateaaceaggeecageteggeatetteaag 50 gacttccctggtctgcgctacatagacctgtcagacaaccgcatcagtggagctgtggagccggtggccaccaca ggggaggtggatggtgggaagaaggtetggetgaeateeagggaeeteaeteeaggeeeaetggaeaeeeeeage tctgaggacttcatgccaagctgcaagaacctcagcttcaccttggacctgtcacggaacaacctggtaacagtc cagccagagatgtttgcccagctctcgcgcctccagtgcctgcgcctgagccacaacagcatctcgcaggcggtc aatggctcacagttcgtgccactgaccagcctgcaggtgctggacctgtcccataacaaactggacctgtaccat ggtgtgggccacaacctcagctttgtggcccagctgcccaccctgcgctacctcagcctggcacacaatggcatc cacageegtgtgteccageagetetgeageacetegetgtgggecetggaetteageggeaattecetgageeag atgtgggctgagggagacctctatctccgcttcttccaaggcctgagaagcctaatccggctagacctgtcccag aatcgtctgcataccctcctgccatgcaccctgggcaacctccccaagagcttgcagctgctgcgtctccgtaac cagctgaaggctctgagcaatggcagcctgccttctggcacccagctccagaggctggacgtcagcaggaacagc atcatcttegtggtccctggcttctttgctctggccacgaggctgcgagagctcaacctcagtgccaacgccctc aggacagaggagccctcctggtttggtttcctagcaggctcccttgaagtcctagatgtgagcgccaaccctctg  $\verb|cactgcgcctgtgggcagcctttgtggacttcctgctgcaggttcaggctgccgtgcctggtctgcccagccgc|\\$ gtcaagtgtggcagtccgggccagctccagggccgcagcatcttcgcacaagacctgcgcctctgcctggacaag tccctctcctgggactgttttggtctctcattgctggttgtgggcctgggcctggccatgcctatgttgcaccac ctctgcggctgggacctctggtactgcttccacctgggcctggcctggctgccccggcgggggtggcagcggggc gcggatgccctgagctatgatgcctttgtggtcttcgacaaggcacagagcgcagttggccgactgggtgtacaat gaactgcgggtgcggctagaggagcgccgtgggcgccggggcgctccgcctgtgtctggaggagcgtgactggcta cctqqcaaqacqctqttcqaaaacctgtgggcctcagtctacagcagccgcaagatgctgttttgtgctggcccac acqqaccaqqtcaqtgqcctcttgcgtgccaqcttcctgctggcccagcagcgtctgctggaggaccgcaaggac gttgtggtgctggtaatcctgagccctgacgccggcgttcccgttacgtgcggctgcgccagcgcctctgccgc cagagtgtcctcttctggccccaccagcctagtggccagcgcagcttctgggcccagctaggcatggccctgacc agggacaacegccacttetataaccagaacttetgccggggcccgacgatggctgagtagcacagagtgacagcc  ${\tt tggcatgtacaacccccagccctgaccttgcctctctgcctatgatgcccagtctgcctcactctgtgacgcccc}$ tgctctgcctccgccaccctcacccctggcatacagcaggcactcaataaatgccactggcaggccaaacagcca aaaaaaaaaaaaa

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## SEQ.ID NO:16 (Equine TLR9)

atgggccttgccatggtgccctgcagccctgtctctcctggtgcaggcggccatgctgtgccgtggctcttgccatggcc caaggcaccetgcctgcctgtgagctccaggccctggtgaactgcaactgcctgtbacctg aagteegtgeeceaetteteageageaceegggacaatgteaceageettteettgeteteaacegeate aagteegtgeeceactteteageageaceeegggacaatgteaceageettteettgeteteeaacegcate 1247 150 4 4  ${\tt agccgcaccaacatcctgcagctagaccccaccagcctcacgggcctgcatgccctgcgcttcctatacatggates}$ ggcaactgctactacaagaacccctgcgggcgggccctggaggtggccccaggcgccctccttggcctgggcaac 35 ctcacccactgtcactcaagtacaacaacctcacaacggtgcccgcagcctgccccctagcctggagtacctg ctqttqtcctacaaccacattqtcaccctgqcacctgaggacctgqccaatctgactgccctgcgtqtgctcgat qtqqqtggaaactgccgccgctgtgaccatgcacgcaacccctgcgtggagtgcccacataaattcccccagctg cactccgacaccttcagccacctaagccgcctagaaggcctcgtgttgaaggatagttctctctaccagctgaac 40 aaaaccaaggcattccagggcctggcccagctgcgaagactcaacttgtccttcaattaccataagaaggtgtcc ttccgctcactcagecagaagacgctccagecactggcccgcctgcccatgctccagcgtctgtatctgcagatg aacttcatcaaccaggcccagctcggcatcttcaaggacttccctggtctgcgctacatagacctgtcagacaac cgcatcagtggagctgtggagccggtggccaccacaggggaggtggatggtgggaagaagatgtggctgacatcc 45 agggacctcactccaggcccactggacacccccagctctgaggacttcatgccaagctgcaagaacctcagcttc ctgcgcctgagccacaacagcatctcgcaggcggtcaatggctcacagttcgtgccactgaccagcctgcaggtg ctggacctgtcccataacaaactggacctgtaccatgggcgctcgtttacggagctgccgcgactggaggccctg gaceteagetacaacagecagecetteageatgeggggtgtggggecacaaceteagetttgtggeceagetgeee 50 accetgegetaceteageetggeacaeaatggeateeacageegtgtgteeeageagetetgeageacetegetg tgggccctggacttcagcggcaattccctgagccagatgtgggctgagggagacctctatctccgcttcttccaa ggcctgagaagcctaatccggctagacctgtcccagaatcgtctgcataccctcctgccatgcaccctgggcaac ctccccaagagcttgcagctgctgcgtctccgtaacaattacctggccttcttcaattggagcagcctgaccctc acccagetecagaggetggaegteageaggaacageateatettegtggtecetggettetttgetetggeeaeg aggctgcgagagctcaacctcagtgccaacgccctcaggacagaggagccctcctggttttggtttcctagcaggc tcccttgaagtcctagatgtgagcgccaaccctctgcactgcgcctgtggggcagcctttgtggacttcctgctg

caggttcaggctgccgtgcctggtctgcccagccgcgtcaagtgtggcagtccgggccagctccagggccgcagcatcttcgcacaagacctgcgcctctgcctggacaagtccctctcctgggactgttttggt

#### SEQ ID NO:17 (Ovine TLR9)

5 MGPYCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGAPRANVTSLSLISNRIH
HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS
RTSILVLGPTHFTGLHALRFLYMDGNCYYKNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL
LSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK
DWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSFGGLVSLEKLDMHGIFF

10 RSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFVDLSDNRISGAARPVAALGEVDSGVEVWRWPR
GLAPGPLAAVSAKDFMPSCNLNFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTRLRVLD
LSYNKLDLYHGRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA
LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQLDLSKNHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP
QLEALDLAGNQLKALSNGSLPPGTRLQKLDVSSNSIGFVTPGFFVLANRLKELNLSANALKTVDPFWFGRLTETL

15 NILDVSANPLHCACGAAFVDFLLEMQAAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFGFSLLMVA
LGLAVPMLHHLCGWDLWYCFHLCLAHLPRRRRQRGEDTLLYDAFVVFDKAQSAVADWVYNELRVQLEERRGRRAL
RLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPAAYRSR
YVRLRQRLCRQSVLLWPHQPSGQGSFWANLGMALTRDNRHFYNRNFCRGPTTAE

## 20 SEQ ID NO:18 (Ovine TLR9)

MGPYCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGAPRANVTSLSLISNRIH
HLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFLAVPTLEELNLSYNGITTVPALPSSLVSLSLS
RTSILVLGPTHFTGLHALRFLYMDGNCYYKNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLL
LSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLEK

25 DWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSFGGLVSLEKLDMHGIFF
RSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFVDLSDNRISGAARPVAALGEVDSGVEVWRWPR
CCLAPGPLAAVSAKDEMPSGNENFTLDLSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTRLRVLD
LSYNKLDLYHGRSFTELPQBEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSASLRA
LDFSGNSLSQMWAEGDLYLCFFKGLRNLVQBDLSKNHLHTLLPRHLDNLPKSLRQLRLRDNNLAFFNWSSLTVLP
30 QEEALDLAGNQEKALSNGSLPPGTRLQKLDVSSNSIGFVTPGFFVLANRLKELNLSANALKTVDPFWFGRLTETL
NILDVSANPLHCACGAAFVDFLLEMQAAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFG

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Buckey St. B. William

## SEQ ID NO:19 (Ovine TLR9)

gtcggcacgggaagtgagcgccaagcatccttccctgcagctgccgcccaacttgcccgccagaccctctggaga 35 agccgcattccctgccatgggcccctactgtgccccgcacccctttctctctggtgcaggcggcggcgctggc agcagccctggcccagggcaccctgcctgccttcctgccctgtgagctccagcccggggtaaggtgaactgcaa etggetgtteetgaagtetgtgeegegetttteggeeggageeeeeegggeeaatgteaeeageeteteettaat ctccaaccgcatccaccttgcacgactctgacttcgtccacctgtccaacctgcgggtcctcaacctcaagtg gaactgcccgccggcctcagccccatgcacttcccctgccgcatgaccatcgagcccaacaccttcctggc  ${\tt tctgtacatggacggcaactgctactataagaacccctgccagcaggccgtggaggtggccccaggcgccctcct}$ tggcctgggcaacctcacgcacctgtcgctcaagtacaaccatcacggaggtgccccgccgcctgcccccag cctggacaccctgctgctgtcctacaaccacatcatcaccctggcacccgaggacctggccaatctgactgccct gcgtgtgcttgatgtgggcgggaactgccgccgctgcgaccacgcccgcaacccctgcagggagtgcccaaagaa cttccccaagetgcaccetgacacettcagccacetgagecgcetegaaggcetggtgttgaaggacagttctet ctacaaactagagaaagactggttccgoggcctgggcaggctccaagtgctcgacctgagtgagaacttcctcta tgactacatcaccaagaccaccatcttcaggaacctgacccagctgcgcagactcaacctgtccttcaattacca caagaaggtgtccttcgcccacctgcaactggcaccctcctttgggggcctggtgtccctggagaagctggacat gcacggcatcttcttccgctccctcaccaacaccacgctccggccgctgacccagctgcccaagctccagagtct gagtctgcagctgaacttcatcaaccaggccgagctcagcatctttgggggccttcccgagcctgctcttcgtgga cctgtcggacaaccgcatcagcggagctgcgaggccggtggccgccctcggggaggtggacagcggggtggaagt ctggcggtggcccaggggcctcgctccaggcccgctggccgtcagcgcaaaggacttcatgccaagctgcaa

cctcaacttcaccttggacctgtcacggaacaacctggtgacgatccagcaggagatgtttacccgcctctcccg cctccagtgcctgcgcctgagccacaacagcatctcgcaggcggttaatggctcgcagttcgtgccgctgacccg  $\verb|cctgcgagtgctcgacctgtcctacaacaagctggacctgtaccatgggcgctcgttcacggagctgccgcagct|$ ggaggcactggacctcagctacaacagccagccttcagcatgcagggcgtgggccacaacctcagcttcgtggc  $\verb|ccagctgccgtccctgcgctacctcagccttgcgcacaacggcatccacagccgcgtgtcacagaagctcagcag|$  $\verb|cgcctcgctgcgccctggacttcagcggcaactccctgagccagatgtgggccgagggagacctctatctctg|$ cttcttcaaaggcttgaggaacctggtccagctggacctgtccaagaaccacctgcacacctcctgcctcgtca cctggataacctgcccaagagcctgcggcagctgcgtctccgggacaataacctggccttcttcaactggagcag cctgactgttctgccccagctggaagccctggatctggcgggaaaccagctgaaggccctgagcaacggcagcct 10 gccacctggcacccggctccagaagctggacgtgagcagcaacagcatcggctttgtgacccctggcttctttgt ccttgccaaccggctgaaagagcttaacctcagcgccaacgccctgaagacagtggatcccttctggttcggtcg  $\verb|cttaacagagaccctgaatatcctagacgtgagcgccaacccgctccactgtgcctgcggggcggcctttgtgga|\\$  $\verb|cttcctgctggagatgcaggcggtgcctgggctgtccaggcgcgtcacgtgtggcagtccgggccagctcca|\\$  $\verb|gggccgcagcatcttcgcacaggacctgcgcctctgcctggatgagaccctctccttggactgcttttgcttctc|\\$  ${\tt gctgctaatggtggcgctggccctggcggtgcccatgctgcaccacctctgtggctgggacctgtggtactgctt}$  $\verb|ccacctgtgtctggcccatttgccccgacggcggcggcggcggggcgaggacaccctgctctacgatgccttcgt|$ ggtcttcgacaaggcgcagagtgcagtggccgactgggtgtacaacgagctccgcgtgcagctggaggagcgccg cgggcgccgggcgctccgcctctgcctggaggagcgagactggctccctggcaagacgctcttcgagaacctgtg  ${\tt ggcctcggtctacagcagccgtaagaccatgttcgtgctggaccacacggaccgggtcagtggcctcctgcgcgc}$ 20  $\verb|cagcttcctgctggcccagcagcgcctgttggaggaccgcaaggatgtcgtggtgctggtgatcctgcgccccgc|\\$  $\verb|cgcctaccggtcccgctacgtgcgcctgcgccagcgcctctgccgccagagcgtcctcctcttggccccaccagcc|\\$ cagtggccagggtagcttctgggccaacctgggcatggccctgaccagggacaaccgccacttctataaccggaa cttctgccggggccccacgacagccgaatagcacagagtgactgcccag

## 25 SEQ ID NO:20 (Ovine TLR9)

atgggcccctactgtgcccgcacccctttctctctggtgcaggcggcggctggcagcagccctggcccag ggcaccctgcctgccttcctgccctgtgagctccagccccggggtaaggtgaactgcaactggctgttcctgaag . totgtgccgcgcttttcggccggagccccccgggccaatgtcaccagcctctccttaatctccaaccgcatccac And the cactegoacgactetgactecgeccacetgeccacetgegggtectcaacetcaagtggaactgeeggeeggee ा । 30 - अ ggcctcagecccatgcacttcccctgccgcatgaccatcgagcccaacaccttcctggctgtgcccaccctggag । अस्ति अस्ति विभागी cgcaccagcatcctggtgctaggccccacccacttcaccggcctgcacgccctgcgctttctgtacatggacggc aactgctactataagaacccctgccagcaggccgtggaggtggccccaggcgccctccttggcctgggcaacctc acgcacctgtcgctcaagtacaaccatcacggaggtgccccgccgcctgcccccagcctggacaccctgctq ctgtcctacaaccacatcatcaccctggcacccgaggacctggccaatctgactgccctgcgtgtgcttgatgtg ggcgggaactgccgccgctgcgaccacgcccgcaacccctgcagggagtgcccaaagaacttccccaagctgcac cctgacaccttcagccacctgagccgcctcgaaggcctggtgttgaaggacagttctctctacaaactagagaaa  ${\tt accaccatcttcaggaacctgacccagctgcgcagactcaacctgtccttcaattaccacaagaaggtgtccttc}$ 40 gcccacctgcaactggcaccctctttgggggcctggtgtccctggagaagctggacatgcacggcatcttcttc cgctccctcaccaacaccacgctccggccgctgacccagctgcccaagctccagagtctgagtctgcagctgaac ttcatcaaccaggccgagctcagcatctttggggccttcccgagcctgctcttcgtggacctgtcggacaaccgc atcagcggagctgcgaggccggtggccgccctcggggaggtggacagcggggtggaagtctggcggtggcccagg  $\verb|ggcctcgctccaggcccgctggccgccgtcagcgcaaaggacttcatgccaagctgcaacctcaaccttg|$ 45  $\tt gacctgtcacggaacaacctggtgacgatccagcaggagatgtttacccgcctctcccgcctccagtgcctgcgc$ ctgagccacaacagcatctcgcaggcggttaatggctcgcagttcgtgccgctgacccgcctgcgagtgctcgac ctgtcctacaacaagctggacctgtaccatgggcgctcgttcacggagctgccgcagctggaggcactggacctc agctacaacagccagcccttcagcatgcagggcgtgggccacaacctcagcttcgtggcccagctgccgtccctg cgctacctcagccttgcgcacaacggcatccacagccgcgtgtcacagaagctcagcagcgcctcgctgcgcgcc 50 ctggacttcagcggcaactccctgagccagatgtgggccgagggagacctctatctctgcttcttcaaaggcttg aggaacctggtccagctggacctgtccaagaaccacctgcacaccctcctgcctcgtcacctggataacctgccc aagageetgeggeagetgegteteegggacaataaeetggeettetteaaetggageageetgaetgttetgeee cagctggaagccctggatctggcgggaaaccagctgaaggccctgagcaacggcagcctgccacctggcacccgg ctccagaagctggacgtgagcagcaacagcatcggctttgtgacccctggcttctttgtccttgccaaccggctg 55 aaagagettaaeeteagegeeaaegeeetgaagaeagtggateeettetggtteggtegettaaeagagaeeetq aatateetagaegtgagegeeaaeeegeteeaetgtgeetgegggggggeetttgtggaetteetgetggagatg

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caggeggeegtgeetgggetgteeaggeggteaegtgtggeagteegggeeageteeagggeegeageatette geacaggaeetgegeetetgeetggatgagaeeeteteettggaetgetttgge

Complete nucleotide and amino acid sequences for canine and feline TLR9 are publicly available. For example, an amino acid sequence for canine TLR9 is available as GenBank accession number BAC65192 and its corresponding nucleotide sequence is available as GenBank accession number AB104899. An amino acid sequence for feline TLR9 is available as GenBank accession number AAN15751 and its corresponding nucleotide sequence is available as GenBank accession number AY137581.

Complete nucleotide and amino acid sequences for canine and feline TLR9 were also determined independently from those available from public databases.

An amino acid sequence of canine TLR9 is provided as SEQ ID NO:21. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:21 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of canine TLR9 (See Figure 1). Amino acids numbered 1-822 of SEQ ID NO:21 are presumptively extracellular domain and correspond to SEQ ID NO:22. SEQ ID NO:23 is a nucleotide sequence of search and the sequence of search and the sequence of search and sequence of canine cDNA encoding amino acids 1-822 of SEQ ID NO:21.

An amino acid sequence of feline TLR9 is provided as SEQ ID NO:25. Based on comparison with known amino acid sequences of human and murine TLR9, it appears that SEQ ID NO:25 includes sequence for at least a majority of the extracellular domain, all of the transmembrane domain, and at least a portion of the intracellular domain of feline TLR9 (See Figure 1). Amino acids numbered 1-820 of SEQ ID NO:25 are presumptively extracellular domain and correspond to SEQ ID NO:26. SEQ ID NO:27 is a nucleotide sequence of feline TLR9 cDNA having an open reading frame corresponding to nucleotides 87-3179. SEQ ID NO:28 is a nucleotide sequence of feline cDNA encoding amino acids 1-820 of SEQ ID NO:25.

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## SEQ ID NO:21 (Canine TLR9)

MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAAPRGNVTSLSLYSNRI HHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFLAVPTLEDLNLSYNSITTVPALPSSLVSLSL SRTNILVLDPATLAGLYALRFLFLDGNCYYKNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYL

- 20 -

LLSYNHI ITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKGFPOLHPNTFGHLSHLEGLVLRDSSLYSLD PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSFGSLLSLOELDIHGIF FRSLSKTTLQSLAHLPMLORLHLQLNFISQAQLSIFGAFPGLRYVDLSDNRISGAAEPAAATGEVEADCGERVWP QSRDLALGPLGTPGSEAFMPSCRTLNFTLDLSRNNLVTVOPEMFVRLARLOCLGLSHNS I SOAVNGSOFVPLSNL RVLDLSHNKLDLYHGRSFTELPRLEALDLSYNSOPFSMRGVGHNLSFVAOLPALRYLSLAHNGIHSRVSOOLRSA SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVOLDLSQNRLHTLLPRNLDNLPKSLRLLRLRDNYLAFFNWSSL ALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVPSFFALAVRLRELNLSANALKTVEPSWFGSL  ${\tt AGALKVLDVTANPLHCACGATFVDFLLEVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFSLSL}$ LAVALSLAVPMLHQLCGWDLWYCFHLCLAWLPRRGRRRGVDALAYDAFVVFDKAOSSVADWVYNELRVOLEERRG RRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQORLLEDRKDVVVLVILCPDA HRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNRHFYNQNFCRGPTTA

#### SEQ ID NO:22 (Canine TLR9)

MGPCRGALHPLSLLVOAAALALAOGTLPAFLPCELOPHGLVNCNWLFLKSVPRFSAAAPRGNVTSLSLYSNRT 15 HHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFLAVPTLEDLNLSYNSITTVPALPSSLVSLSL SRTNILVLDPATLAGLYALRFLFLDGNCYYKNPCOOALOVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYL LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCRECPKGFPOLHPNTFGHLSHLEGLVLRDSSLYSLD PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSFGSLLSLQELDIHGIF  ${\tt FRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYVDLSDNRISGAAEPAAATGEVEADCGERVWP}$ 20 QSRDLALGPLGTPGSEAFMPSCRTLNFTLDLSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNL RVLDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA SLRALDFSGNTLSQMWAEGDLYLRFFQGLRSLVQLDLSQNRLHTLLPRNLDNLPKSLRLLRLRDNYLAFFNWSSL ALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVPSFFALAVRLRELNLSANALKTVEPSWFGSL AGALKVLDVTANPLHCACGATFVDFLLEVQAAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFS 25

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# SEQ ID NO 23 (Canine TLR9)

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aatggcagcttgcccaacggcacccagctccagaggctggacctcagcggccaacagcatcggcttcgtggtcccc agettttttgeeetggeegtgaggettegagageteaaeeteagegeeaaegeeeteaagaeggtggageeetee tggtttggttccctggcgggtgccctgaaagtcctagacgtgaccgccaaccccttgcattgcgcttgcggcgca ggccagctccagggccgcagcatcttcgcacaggacctgcgcctctgccctggacgaagcgctctcctgggtctqt ttcagcctctcgctgctgtgtgccctgagcctggctgtgcccatgctgcaccagctctgtggctgggacctc gacgccttcgtggtcttcgacaaggcgcagagctcggtggcggactgggtgtacaatgagctgcgggtacaqcta gaggagcgccgtgggcgccgggcgctacgcctgtgtctggaggaacgtgactgggtacccggcaaaaccctcttc gagaacctctgggcctcagtttacagcagccgcaagacgctgtttgtgctggcccgcacggacagagtcagcggc ctcctgcgtgccagcttcctgctggcccaacagcgcctgctggaggaccgcaaggacgtcgtggtgctggtgatc ctgtgccccgacgcccaccgctcccgctatgtgcggctgcgccagcgcctctgccgccagagtgtcctcctctgg ccccaccagcccagtggccagcgcagcttctgggcccagctgggcacggccctgaccagggacaaccgccacttc tacaaccagaacttctgccggggccccacgacagcctgataggcagacagcccagcaccttcgcgcccctacacc 15 etgeetgtetgtetgggatgeeegaeetgetggetetaeaeegeegetetgteteeeetaeaeeeageeetggea taaagcgaccgctcaataaatgctgctggtagac

#### SEQ ID NO:24 (Canine TLR9)

atgggcccctgccgtggcgccctgcaccccctgtctctcctggtgcaggctgccgcgctagccctggccctggcc 20 cagggeaccetgeetgeetteetgeeetgtgageteeageeeeatggeetggtgaactgeaaetggetgtteete aagtccgtgccccgcttctcggcagctgcaccccgcggtaacgtcaccagcctttccttgtactccaaccgcatc gccagcctcagccccatgcactttccctgtcacatgaccattgagcccaacaccttcctggctgtgcccacccta 25 @agccgcaccaacatcctggtgctggaccctgccaccctggcaggcctttatgccctgcgcttcctgttcctggat #ggcaactgctactacaagaacccctgccagcaggccctgcaggtggccccaggtgccctcctgggcctgggcaac - ctcacacacctgtcactcaagtacaacaacctcaccgtggtgccgcgggggcctgccccccaqcctqqaqtacctq ctcttgtcctacaaccacatcatcaccctggcacctgaggacctggccaatctgactgccctqcqtqtcctcqat wigigggtgggaactigtegeegetgtgaccatgeeggtaacceetgeagggagtgeeceaagggetteeceeagetg \*\*aaaaccaaagccttctacggcctggcccggctgcgcagactcaacctgtccttcaattatcataagaaggtgtcc \*\*ttccgctcgctcagcaagaccacgctccagtcgctggcccacctgcccatgctccagcgtctgcatctgcagttg 35 aaactttatcagccaggcccagctcagcatcttcggcgccttccctggactgcggtacgtggacttgtcagacaac .cgcatcagtggagctgcagagcccgcggctgccacaggggaggtagaggcagactgtggggagagagtctggcca · cagtcccgggaccttgctctgggcccactgggcacccccggctcagaggccttcatgccgaqctgcaggaccttc aacttcaccttggacctgtctcggaacaacctagtgactgttcagccggagatgtttgtccggctggcgcqcctc cagtgcctgggcctgagccacaacagcatctcgcaggcggtcaatggctcgcagttcgtgcctctgagcaacctq 40 cgggtgctggacctgtcccataacaagctggacctgtaccacgggcgctcgttcacggagctgccgcggctqgaq gccttggacctcagctacaacagccagcccttcagcatgcggggcgtgggccacaatctcagctttgtggcacag ctgccagccctgcgctacctcagcctggcgcacaatggcatccacagccgcgtgtcccagcagctccgcagcgcc tegeteegggeeetggaetteagtggeaataceetgageeagatgtgggeegaggggagaeetetateteegette ttccaaggcctgagaagcctggttcagctggacctgtcccagaatcgcctqcataccctcctqccacqcaacctq gacaacctccccaagagcctgcggctcctgcgqctccqtqacaattacctgqctttcttcaactqqaqcaqcctq gccctcctacccaagctggaagccctggacctggcgggaaaccagctgaaggccctgagcaatggcagcttqccc aacggcacccagctccagaggctggacctcagcggcaacaqcatcggcttcgtggtccccaqctttttttqccctq gegggtgecetgaaagteetagaegtgaeegeeaaeeeettgeattgegettgeggegeaaeettegtggaette 50 ttgctggaggtgcaggctgcggtgcccggcctgcctagccgtgtcaagtgcggcagcccgggccagctccagggc egeageatettegeaeaggaeetgegeetetgeetggaegaagegeteteetgggtetgttteage

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#### SEQ ID NO:25 (Feline TLR9)

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MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAAPRGNVTSLSLYSNRI HHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFLAVPTLEELNLSYNSITTVPALPSSLVSLSL 10

SRTNILVLDPANLAGLHSLRFLFLDGNCYYKNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYL
LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN
PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSFGSLLSLQQLDMHGIF
FRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYVDLSDNRISGAMELAAATGEVDGGERVRLPS
GDLALGPPGTPSSEGFMPGCKTLNFTLDLSRNNLVTIQPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQV
LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASL
RALDFSGNALSRMWAEGDLYLHFFRGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLRLLRLRDNYLAFFNWSSLVL
LPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVASSFFALATRLRELNLSANALKTVEPSWFGSLAG
TLKVLDVTGNPLHCACGAAFVDFLLEVQAAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDEALSWDCFGLSLLT
VALGLAVPMLHHLCGWDLWYCFHLCLAWLPRRGRRRGADALPYDAFVVFDKAQSAVADWVYNBLRVRLEERRGRR
ALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILRPDAHR
SRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNQHFYNQNFCRGPTTAE

## SEQ ID NO:26 (Feline TLR9)

MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAAPRGNVTSLSLYSNRI
HHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFLAVPTLEELNLSYNSITTVPALPSSLVSLSL
SRTNILVLDPANLAGLHSLRFLFLDGNCYYKNPCPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYL
LLSYNHIITLAPEDLANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN
PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSFGSLLSLQQLDMHGIF
PRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYVDLSDNRISGAMELAAATGEVDGGERVRLPS
GDLALGPPGTPSSEGFMPGCKTLNFTLDLSRNNLVTIQPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQV
LDLSHNKLDLYHGRSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSASL
RALDFSGNALSRMWAEGDLYLHFFRGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLRLLRLRDNYLAFFNWSSLVL
LPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVASSFFALATRLRELNLSANALKTVEPSWFGSLAG
TLKVLDVTGNPLHCACGAAFVDFLLEVQAAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDBALSWDCFG

# SEQ ID NO:27 (Feline TLR9)

 ${\tt agggtctgcgagctccaggcattcttctctgccatcgctgcccagtctgccatccagaccctctggagaagcccc}$ cactccctqtcatqqqcccctqccatqqcgccctqcacccctqtctctcctgqtqcaggctqccgcqctqgccg tggccctggcccagggcaccctgcctttctgccctgtgagctccagcgccacggcctggtgaattgcgact qqctqttcctcaaqtccqtgccccacttctcggcggcagcgccccgtggtaacgtcaccagcctttccctgtact ccaaccgcatccaccacctccacgactccgactttgtccacctgtccagcctgcggcgtctcaacctcaaatgga actqcccacccqccaqcctcaqccccatqcacttcccctqtcacatgaccattgagcccacaccttcctggccg tgcccaccctqqaqqaqctqaacctqaqctacaacagcatcacgacagtacccgccctgcccagttccctcgtgt 35 ccctqtccttqaqccqtaccaacatcctqqtgctggaccctgccaacctcgcagggctgcactccctgcgctttc tqttcctqqatqqcaactqctactacaagaacccctgcccgcaggccctgcaggtggccccgggcgccctccttg qcctqqqcaaccttacqcacctqtcactcaagtacaacaacctcactgcggtgccccgcggcctgcccccagcc tggagtacctgctattgtcctacaaccacatcatcaccctggcacctgaggacctggccaacctgaccgccctgc gtgtgctcgatgtgggtgggaactgccgtcgctgtgaccacgcccgcaacccctgtatggagtgccccaagggct 40 actgcatcaccaaaaccacagccttccagggcctggcccagctgcgcagactcaacttgtctttcaattaccaca agaaggtgtcctttgcccacctgcatctggcgccctccttcgggagcctgctctccctgcagcagctggacatgc atggcatcttcttccgctcgctcagcgagaccacgctccggtcgctggtccacctgcccatgctccagagtctgc 45 acctgcagatgaacttcatcaatcaggcccagctcagcatcttcggggccttccctggcctgcgatacgtggacc tgtcagacaaccgcataagtggagccatggagctggcggctgccacgggggaggtggatggtgggggagagagtcc ggctgccatctggggacctagctctgggcccaccgggcacccctagctccgagggcttcatgccaggctgcaaga ccctcaacttcaccttqqacctgtcacqqaacaacctagtqacaatccagccagagatgtttgcccggctctcgc qcctccaqtqcctqctcctqagccqcaacaqcatctcgcaqqcaqtcaacgqctcacaatttatgccgctgacca 50 qcctqcaqqtqctqqacctqtcccataacaaqctgqacctqtaccatgqgcgctctttcacggagctgccgcggc tggaggccttggacctcagctacaacagccagcccttcagcatgcagggcqtgggtcacaacctcagctttqtgg cacagetqeeqqeeetqeqetateteaqeetqqeqcacaacqacatecacaqeeqtqtqteecaqeaqetetqea gcgcctcgctgcgggccttggacttcagcggcaatgccttgagccggatgtgggccgagggagacctgtatctcc acttettecqaqqeetqaggageetqqteeqgttggatetqteecagaategeetgcataccetettgeeacgea 55 ccctqqacaacctccccaagagcctgcggctgctgcgtctccgtgacaattatctggctttcttcaactggagca

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## SEQ ID NO:28 (Feline TLR9)

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ा राष्ट्रका (स्टाउंग) हो। जन्म

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Complete nucleotide and amino acid sequences for murine and human TLR9 are publicly available. For example, an amino acid sequence of murine TLR9 is available as

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GenBank accession no. AAK29625, provided as SEQ ID NO:29. Amino acids numbered 1-821 of SEQ ID NO:29 presumptively include the entire extracellular domain and correspond to SEQ ID NO:30. SEQ ID NO:31 corresponds to GenBank accession number AF348140, which is a nucleotide sequence of murine TLR9 cDNA. SEQ ID NO:32 is a nucleotide sequence of murine cDNA encoding amino acids 1-821 of SEQ ID NO:29.

An amino acid sequence of human TLR9 is available as GenBank accession no. AAF78037, provided as SEQ ID NO:33. Amino acids numbered 1-820 of SEQ ID NO:33 presumptively include the entire extracellular domain and correspond to SEQ ID NO:34. SEQ ID NO:35 corresponds to GenBank accession number AF245704, which is a nucleotide sequence of human TLR9 cDNA. SEQ ID NO:36 is a nucleotide sequence of human cDNA encoding amino acids 1-820 of SEQ ID NO:33.

## SEQ ID NO:29 (Murine TLR9)

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WO 2004/026888

MVLRRRTLHPLSLLVQAAVLAETLALGTLPAFLPCELKPHGLVDCNWLFLKSVPRFSAAASCSNITRLSLISNRI HHLHNSDFVHLSNLRQLNLKWNCPPTGLSPLHFSCHMTIEPRTFLAMRTLEELNLSYNGITTVPRLPSSLVNLSL  ${\tt SHTNILVLDANSLAGLYSLRVLFMDGNCYYKNPCTGAVKVTPGALLGLSNLTHLSLKYNNLTKVPRQLPPSLEYL}$ LVSYNLIVKLGPEDLANLTSLRVLDVGGNCRRCDHAPNPCIECGQKSLHLHPETFHHLSHLEGLVLKDSSLHTIN SSWFQGLVNLSVLDLSENFLYESINHTNAFQNLTRLRKLNLSFNYRKKVSFARLHLASSFKNLVSLQELNMNGIF FRSLNKYTLRWLADLPKLHTLHLQMNFINQAQLSIFGTFRALRFVDLSDNRISGPSTLSEATPEEADDAEQEELL 20 SADPHPÄPLSTPÄSKNFMDRCKNPKFTMDLSRNNLVTIKPEMFVNLSRLQCLSLSHNSIAQAVNGSQFLPLTNLQ VLDLSHNKLDLYHWKSFSELPQLQALDLSYNSQPFSMKGIGHNFSFVAHLSMLHSLSLAHNDIHTRVSSHLNSNS VRFLDFSGNGMGRMWDEGGLYLHFFQGLSGLLKLDLSQNNLHILRPQNLDNLPKSLKLLSLRDNYLSFFNWTSLS FLPNLEVLDLAGNOLKALTNGTLPNGTLLQKLDVSSNSIVSVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV  $\verb|MNLTVLDVRSNPLHCACGAAFVDLLLEVQTKVPGLANGVKCGSPGQLQGRS1FAQDLRLCLDEVLSWDCFGLSLL|\\$ 25 AVAVGMVVPILHHLCGWDVWYCFHLCLAWLPLLARSRRSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEERRG RRALRLCLEDRDWLPGOTLFENLWASIYGSRKTLFVLAHTDRVSGLLRTSFLLAQQRLLEDRKDVVVLVILRPDA HRSRYVRLRORLCROSVLFWPQQPNGQGGFWAQLSTALTRDNRHFYNQNFCRGPTAE

#### SEO ID NO:30 (Murine TLR9)

MVLRRTLHPLSLLVOAAVLAETLALGTLPAFLPCELKPHGLVDCNWLFLKSVPRFSAAASCSNITRLSLISNRI 30 HHLHNSDFVHLSNLRQLNLKWNCPPTGLSPLHFSCHMTIEPRTFLAMRTLEELNLSYNGITTVPRLPSSLVNLSL SHTNILVLDANSLAGLYSLRVLFMDGNCYYKNPCTGAVKVTPGALLGLSNLTHLSLKYNNLTKVPROLPPSLEYL LVSYNLIVKLGPEDLANLTSLRVLDVGGNCRRCDHAPNPCIECGQKSLHLHPETFHHLSHLEGLVLKDSSLHTLN SSWFOGLVNLSVLDLSENFLYESINHTNAFQNLTRLRKLNLSFNYRKKVSFARLHLASSFKNLVSLQELNMNGIF FRSLNKYTLRWLADLPKLHTLHLQMNFINQAQLSIFGTFRALRFVDLSDNRISGPSTLSEATPEEADDAEQEELL SADPHPAPLSTPASKNFMDRCKNFKFTMDLSRNNLVTIKPEMFVNLSRLQCLSLSHNSIAQAVNGSQFLPLTNLQ VLDLSHNKLDLYHWKSFSELPQLQALDLSYNSQPFSMKGIGHNFSFVAHLSMLHSLSLAHNDIHTRVSSHLNSNS VRFLDFSGNGMGRMWDEGGLYLHFFQGLSGLLKLDLSQNNLHILRPQNLDNLPKSLKLLSLRDNYLSFFNWTSLS FLPNLEVLDLAGNOLKALTNGTLPNGTLLOKLDVSSNSIVSVVPAFFALAVELKEVNLSHNILKTVDRSWFGPIV MNLTVLDVRSNPLHCACGAAFVDLLLEVOTKVPGLANGVKCGSPGQLQGRSIFAQDLRLCLDEVLSWDCFG

#### SEO ID NO:31 (Murine TLR9)

tqtcaqaqggaqcctcgggagaatcctccatctccaacatggttctccgtcgaaggactctgcaccccttgtcc 

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#### SEQ ID NO:31 (Murine TLR9)

45 ctgggtaccctgcctgccttcctaccctgtgagctgaagcctcatggcctggtggactgcaattggctgttcctg aagtetgtaccccgtttctctgcggcagcatcctgctccaacatcacccgcctctccttgatctccaaccgtatc caccacctgcacaactccgacttcgtccacctgtccaacctgcggcagctgaacctcaagtggaactgtccaccc actggccttagccccctgcacttctcttgccacatgaccattgagcccagaaccttcctggctatgcgtacactg gaggagctgaacctgagctataatggtatcaccactgtgccccgactgcccagctccctggtgaatctgagcctg 50  ${\tt agccaccaccatcctggttctagatgctaacagcctcgccggcctatacagcctgcgcgttctcttcatggac}$ gggaactgctactacaagaacccctgcacaggagcggtgaaggtgaccccaggcgccctcctgggcctgagcaat  $\verb|ctcacccatctgtctctgaagtataaccatctcacaaaggtgccccgccaactgcccccagcctggagtacctc|$  $\verb|ctggtgtcctataacctcattgtcaagctggggcctgaagacctggccaatctgacctcccttcgagtacttgat|\\$ gtgggtgggaattgccgtcgctgcgaccatgccccaatccctgtatagaatgtggccaaaagtccctccacctg 55 caccctgagaccttccatcacctgagccatctggaaggcctggtgctgaaggacagctctctccatacactgaac  ${\tt tcttcctggttccaaggtctggtcaacctctcggtgctggacctaagcgagaactttctctatgaaagcatcaac}$ cacaccaatgcctttcagaacctaacccgcctgcgcaagctcaacctgtccttcaattaccgcaagaaggtatcc

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#### SEQ ID NO:33 (Human TLR9)

MGFCRSALHPLSLLVOAIMLAMTLALGTLPAFLPCELOPHGLVNCNWLFLKSVPHFSMAAPRGNVTSLSLSSNRI HHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFLAVPTLEKLNLSYNNIMTVPALPKSLISLSL Company Compan BY WELLEY WAS ASWINGLIGHT OF THE STATE OF TH FRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYVDLSDNRISGASELTATMGEADGGEKVWLQP CONTROL OF THE CONTRO orto deregation of LDL Sriked By Hehspielprieaed Lsynsopfic Mogovich Psyvall Rill Religious Color Colo raldescnalghmans and the company of the control of 19 Noving States Live LPKLEVLDLAGNREKALTNGSEPAGTRERREDVSCNSISFVAPGFFSKAKEEREENESANALKTVDHSWFGPLAS ALQILDVSANPLHCACGAAFMDFLLEVQAAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFALSLLA VALGLGVPMLHHLCGWDLWYCFHLCLAWLPWRGRQSGRDEDALPYDAFVVFDKTQSAVADWVYNELRGQLEECRG  ${\tt RWALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRLLEDRKDVVVLVILSPDG}$ RRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNHHFYNRNFCQGPTAE

# SEQ ID NO:34 (Human TLR9)

MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAAPRGNVTSLSLSSNRI HHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFLAVPTLEBLNLSYNNIMTVPALPKSLISLSL SHTNILMLDSASLAGLHALRFLFMDGNCYYKNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYL LLSYNRIVKLAPEDLANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPQLHPDTFSHLSRLEGLVLKDSSLSWLN ASWFRGLGNLRVLDLSENFLYKCITKTKAPQGLTQLRKLNLSFNYQKRVSFAHLSLAPSFGSLVALKELDMHGIF FRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYVDLSDNRISGASELTATMGEADGGEKVWLOP GDLAPAPVDTPSSEDFRPNCSTLNFTLDLSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQV LDLSRNKLDLYHEHSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSTSL RALDFSGNALGHMWAEGDLYLHFFQGLSGLIWLDLSQNRLHTLLPQTLRNLPKSLQVLRLRDNYLAFFKWWSLHF LPKLEVLDLAGNRLKALTNGSLPAGTRLRRLDVSCNSISFVAPGFFSKAKELRELNLSANALKTVDHSWFGPLAS ALQILDVSANPLHCACGAAFMDFLLEVQAAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFA

#### SEQ ID NO:35 (Human TLR9) 50

aggctggtataaaaatettaetteetetattetetgageegetgetgeeeetgtgggaagggaeetegagtgtga ageatcettccctgtagetgetgtccagtctgcccgccagaccctctggagaagcccctgcccccagcatgggt ttctgccgcagcgccctgcacccgctgtctctcctggtgcaggccatcatqctqqccatqaccctqqct

accttgcctgccttcctaccctgtgagctccagccccacggcctggtgaactgcaactggctgttcctgaagtct gtgccccacttctccatggcagcacccgtggcaatgtcaccagcctttccttgtcctccaaccgcatccaccac ctccatgattctgacttttgcccacctgcccagcctgcggcatctcaacctcaagtggaactgcccggcttggc ctcagccccatgcacttcccctgccacatgaccatcgagcccagcaccttcttggctgtgcccaccctggaagag ctaaacctgagctacaacaacatcatgactgtgcctgcgctgcccaaatccctcatatccctgtccctcagccat accaacatectgatgetagactetgecageetegeeggeetgeatgeeetgegetteetatteatggaeggeaac tgttattacaagaacccctgcaggcaggcactggaggtggccccgggtgccctccttggcctgggcaacctcacc cacctgtcactcaagtacaacatcactgtggtgccccgcaacctgccttccagcctggagtatctgctgttg tectacaacegeategteaaaetggegeetgaggaeetggeeaatetgaeegeeetgegtgtgetegatgtggge ggaaattgccgccgctgcgaccacgctcccaacccctgcatggagtgccctcgtcacttcccccagctacatccc 10 aaggeetteeagggeetaacaagetgegeaagettaacetgteetteaattaecaaaagagggtgteetttgee cacctgtctctggccccttccttcgggagcctggtcgccctgaaggagctggacatgcacggcatcttcttccgc 15 tcactcgatgagaccacgctccggccactggcccgcctgcccatgctccagactctgcgtctgcagatgaacttc atcaaccaggcccagctcggcatcttcagggccttccctggcctgcgctacgtggacctgtcggacaaccgcatc agcggagcttccggagctgacagccaccatgggggaggcagatggaggggagaaaggtctggctgcagcctggggac  $\verb|cttgctccggccccagtggacactcccagctctgaagacttcaggcccaactgcagcaccctcaacttcaccttg|$ gatctgtcacggaacaacctggtgaccgtgcagccggagatgtttgcccagctctcgcacctgcagtgcctgcgc 20 ctgagccacaactgcatctcgcaggcagtcaatggctcccagttcctgccgctgaccggtctgcaggtgctagac  $\verb|ctgtcccgcaataagctggacctctaccacgagcactcattcacggagctaccgcgactggagccctggacctc|$  ${\tt agctacaacagccagccctttggcatgcagggcgtgggccacaacttcagcttcgtggctcacctgcgcaccctg}$ cgccacctcagcctggcccacaacaacatccacagccaagtgtcccagcagctctgcagtacgtcgctgcgggcc ctggacttcagcggcaatgcactgggccatatgtgggccgagggagacctctatctgcacttcttccaaggcctg ageggtttgatetggetggaettgteceagaaeegeetgeaeaeeeteetgeeeeaaaeeetgegeaaeeteeee \*aagagcctacaggtgctgcgtctccgtgacaattacctggccttctttaagtggtggagcctccacttcctgccc potecggaggctggatgtcagctgcaacagcatcagcttcgtggcccccggcttcttttccaaggccaaggagctg .cqaqagctcaaccttagcgccaacgccctcaagacagtggaccactcctggtttgggcccctggcgagtgccctg :×30 \*\*caaatactagatgtaagcgccaaccctctgcactgcgcctgtggggcggcctttatggacttcctgctggaggtg \*\*caggctgccggtgccgggtctggccagccgggtgaagtgtggcagtccgggccagctccagggcctcagcatcttt gcacaggacctgcgcctctgcctggatgaggccctctcctgggactgtttcgccctctcgctgctgctgtggct \*\*etgggcctgggtgtgcccatgctgcatcacctctgtggctgggacctctggtactgcttccacctgtgcctggcc - toggetteeetggeggggggggeaaagtgggegagatgaggatgeeetgeeetaegatgeettegtggtettegae 35 - aaaacgcagagcgcagtggcagactgggtgtacaacgagcttcgggggcagctggaggagtgccgtgggcgctgg gcactccgcctgtgcctggaggaacgcgactggctgcctggcaaaaccctctttgagaacctgtgggcctcggtc tatggcagccgcaagacgctgtttgtgctggcccacacggaccgggtcagtggtctctttgcgcgccagcttcctg ctqqcccaqcaqcqcctqctqqaqqaccqcaaqqacgtcgtggtgctggtgatcctgagccctgacggccgccgc tcccgctacgtgcggctgcgccagcgcctctgccgccagagtgtcctcctctggccccaccagcccagtggtcag 40 cgcagcttctgggcccagctgggcatggccctgaccagggacaaccaccacttctataaccggaacttctgccag tggtctgaccctccctgctcgcctccctcaccccacacctgacacagagca

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## SEQ ID NO:36 (Human TLR9)

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aaaaccaaggccttccagggcctaacacagctgcgcaagcttaacctgtccttcaattaccaaaagagggtgtcc tttgcccacctgtctctggccccttccttcgggagcctggtcgccctgaaggagctggacatgcacggcatcttc ttccgctcactcgatgagaccacgctccggccactggcccgcctgcccatgctccagactctgcgtctgcagatg aacttcatcaaccaggcccagctcggcatcttcagggccttccctggcctgcgctacgtggacctgtcggacaac ggggaccttgctccggccccagtggacactcccagctctgaagacttcaggcccaactgcagcaccctcaacttc accttggatctgtcacggaacaacctggtgaccgtgcagccggagatgtttgcccagctctcgcacctgcagtgc etgegeetgageeacaaetgeatetegeaggeagteaatggeteecagtteetgeegetgaeeggtetgeaggtg ctagacctgtcccgcaataagctggacctctaccacgagcactcattcacggagctaccgcgactggaggccctg  $\tt gacctcagctacaacagccagccctttggcatgcagggcgtgggccacaacttcagcttcgtggctcacctgcgc$ accetgegeeaceteageetggeecacaacaacatecacagecaagtqteecageagetetgeagtacqtegetq cgggccctggacttcagcggcaatgcactgggccatatgtgggccgagggagacctctatctgcacttcttccaa ggcctgagcggtttgatctggctggacttgtcccagaaccgcctgcacaccctcctgccccaaaccctqcgcaac ctccccaagagcctacaggtgctgcgtctccgtgacaattacctggccttctttaagtggtggagcctccacttc acceggeteeggaggetggatgteagetgeaacageateagettegtggeeeeeggettetttteeaaggeeaaq gagetgegagageteaacettagegecaacgeceteaagacagtggaccacteetggtttgggeceetggegagt gccctgcaaatactagatgtaagcgccaaccctctgcactgcgcctgtggggcggcctttatggacttcctgctg gaggtgcaggctgccgtgcccggtctgcccagccgggtgaagtgtgggcagtccgggccagctccagggcctcagc atctttgcacaggacctgcgcctctgcctggatgaggccctctcctgggactgtttcgcc

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In addition to the foregoing native rat, porcine, bovine, equine, and ovine TLR9 polypeptides and nucleic acid molecules encoding them, chimeric TLR9 polypeptides and nucleic acid molecules encoding them are provided by the invention. The chimeric polypeptides include at least one amino acid substitution based on a comparison of conserved and non-conserved amino acids among at least two of rat, murine, porcine, bovine, equine, ovine, canine, feline, and human TLR9. The information contained in a multiple sequence alignment of these various TLR9 polypeptide sequences, provided for example in Figure 1, can be used to identify and select individual amino acid positions and even individual amino acids to substitute in designing a chimeric TLR9. The substitution or substitutions can be effected using methods known to those of ordinary skill in molecular biology. Nucleic acids encoding the native or chimeric polypeptides of the invention can be inserted into an expression vector and used to express TLR9 polypeptide.

A conservative amino acid substitution shall refer to a substitution of a first amino acid for a second amino acid, wherein side chains of the first amino acid and the second amino acid share similar features in terms of hydrophobicity, size, aromaticity, or tendency to alter conformation. For example, conservative amino acid substitutions generally may be made between members within each of the following groups: hydrophobic (A, I, L, M, V), neutral (C, S, T), acidic (D, E), basic (H, K, N, Q, R), and aromatic (F, W, Y). A non-conservative amino acid substitution refers to any other amino acid substitution.

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those of ordinary skill in the art.

An expression vector for TLR9 will include at least a nucleotide sequence coding for a TLR9, or a fragment thereof coding for a functional TLR9 polypeptide, operably linked to a gene expression sequence which can direct the expression of the TLR9 nucleic acid within a eukaryotic or prokaryotic cell. A "gene expression sequence" is any regulatory nucleotide sequence, such as a promoter sequence or promoter-enhancer combination, which facilitates the efficient transcription and translation of the nucleic acid to which it is operably linked. With respect to TLR9 nucleic acid, the "gene expression sequence" is any regulatory nucleotide sequence, such as a promoter sequence or promoter-enhancer combination, which facilitates the efficient transcription and translation of the TLR9 nucleic acid to which it is operably linked. The gene expression sequence may, for example, be a mammalian or viral promoter, such as a constitutive or inducible promoter. Constitutive mammalian promoters include, but are not limited to, the promoters for the following genes: hypoxanthine phosphoribosyl transferase (HPRT), adenosine deaminase, pyruvate kinase, β-actin promoter, and other constitutive promoters. Exemplary viral promoters which function constitutively in 15 \*\*eukaryotic; cells; include, for example, promoters from the simian virus (e.g., SV40), papillomavirus, adenovirus, human immunodeficiency virus (HIV), Rous sarcoma virus (RSV) cytomegalovirus (CMV), the long terminal repeats (LTR) of Moloney murine eleukemia virus and other retroviruses, and the thymidine kinase (TK) promoter of herpes simplex virus. Other constitutive promoters are known to those of ordinary skill in the art. The promoters useful as gene expression sequences of the invention also include inducible promoters. Inducible promoters are expressed in the presence of an inducing agent. For example, the metallothionein (MT) promoter is induced to promote transcription and translation in the presence of certain metal ions. Other inducible promoters are known to

In general, the gene expression sequence shall include, as necessary, 5' nontranscribing and 5' non-translating sequences involved with the initiation of transcription and translation, respectively, such as a TATA box, capping sequence, CAAT sequence, and the like. Especially, such 5' non-transcribing sequences will include a promoter region which includes a promoter sequence for transcriptional control of the operably joined nucleic acid coding sequence for a TLR9 polypeptide. The gene expression sequences optionally include enhancer sequences or upstream activator sequences as desired.

Generally a nucleic acid coding sequence and a gene expression sequence are said to be "operably linked" when they are covalently linked in such a way as to place the transcription and/or translation of the nucleic acid coding sequence under the influence or control of the gene expression sequence. Thus the TLR9 nucleic acid coding sequence and the gene expression sequence are said to be "operably linked" when they are covalently linked in such a way as to place the transcription and/or translation of the TLR9 nucleic acid coding sequence under the influence or control of the gene expression sequence. If it is desired that the TLR9 sequence be translated into a functional protein, two DNA sequences are said to be operably linked if induction of a promoter in the 5' gene expression sequence results in the transcription of the TLR9 sequence and if the nature of the linkage between the two DNA sequences does not (1) result in the introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region to direct the transcription of the TLR9 sequence, or (3) interfere with the ability of the corresponding RNA transcript to be translated into a protein. Thus, a gene expression sequence would be operably linked to a TLR9 nucleic acid sequence if the gene expression sequence were capable of effecting transcription of that TLR9 nucleic acid sequence such that the resulting transcript might be translated into the desired TLR9 protein or polypeptide.

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polypeptide. In one embodiment the TLR9 ligand specifically binds a TLR9 polypeptide corresponding to at least a ligand-binding portion of the extracellular domain of TLR9. In most instances a TLR9 ligand will also induce TLR9 signaling when contacted with TLR9 under suitable conditions. TLR9 signaling refers to TLR/IL-1R signal transduction mediated through the TLR9, as described in further detail elsewhere herein. As mentioned above, CpG nucleic acids have been reported to be TLR9 ligands, but TLR9 ligands may include other entities as well, including, for example, small molecules. As also previously mentioned, there appears to be a species-specific preference for at least certain TLR9s and certain CpG motifs. As used herein, a species-preferred CpG DNA refers to a particular CpG DNA that is optimized for signal induction by a TLR9 of a particular species. A CpG DNA that is optimized for signal induction by a TLR9 of a particular species refers to a CpG DNA having a sequence that preferentially binds to and/or induces signaling by TLR9 of that species. For example, a human-preferred CpG DNA shall refer to a CpG DNA that optimally stimulates human TLR9 to signal through its TIR domain. Likewise, a murine-preferred CpG DNA

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shall refer to a CpG DNA that optimally stimulates murine TLR9 to signal through its TIR domain. Examples of human-preferred and murine-preferred CpG DNA are ODN 2006 (SEQ ID NO:58) and 1668 (SEQ ID NO:60), respectively.

The binding and species specificity of TLR9s are believed to be influenced by key amino acids present in the extracellular domain of TLR9. Key amino acids in a TLR9 as used herein refer to those amino acids which contribute significantly to ligand binding and ligand specificity of a particular TLR9 polypeptide.

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A "CpG nucleic acid" or a "CpG immunostimulatory nucleic acid" as used herein is a nucleic acid containing at least one unmethylated CpG dinucleotide (cytosine-guanine dinucleotide sequence, i.e., "CpG DNA" or DNA containing a 5' cytosine followed by 3' guanine and linked by a phosphate bond) which activates a component of the immune system. The entire CpG nucleic acid can be unmethylated or portions may be unmethylated but at least the C of the 5' CG 3' must be unmethylated.

In one embodiment a CpG nucleic acid is represented by at least the formula:

5!-N<sub>1</sub>X<sub>1</sub>CGX<sub>2</sub>N<sub>2</sub>-3'

wherein  $X_1$  and  $X_2$  are nucleotides, N is any nucleotide, and  $N_1$  and  $N_2$  are nucleic acid sequences composed of from about 0-25 N's each. In some embodiments  $X_1$  is adenine, guanine, or thymine and/or  $X_2$  is cytosine, adenine, or thymine. In other embodiments  $X_1$  is cytosine and/or  $X_2$  is guanine.

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\*Nucleic acids having modified backbones, such as phosphorothioate backbones, also fall within the class of immunostimulatory nucleic acids. U.S. Pat. Nos. 5,723,335 and 5,663,153 issued to Hutcherson, et al. and related PCT publication WO95/26204 describe immune stimulation using phosphorothioate oligonucleotide analogues. These patents describe the ability of the phosphorothioate backbone to stimulate an immune response in a non-sequence specific manner.

An immunostimulatory nucleic acid molecule, including for example a CpG DNA, may be double-stranded or single-stranded. Generally, double-stranded molecules may be more stable *in vivo*, while single-stranded molecules may have increased activity. The terms "nucleic acid" and "oligonucleotide" refer to multiple nucleotides (i.e., molecules comprising a sugar (e.g., ribose or deoxyribose) linked to a phosphate group and to an exchangeable organic base, which is either a substituted pyrimidine (e.g., cytosine (C), thymine (T) or uracil (U)) or a substituted purine (e.g., adenine (A) or guanine (G)) or a modified base. As

PCT/US2003/029577 WO 2004/026888

used herein, the terms "nucleic acid" and "oligonucleotide" refer to oligoribonucleotides as well as oligodeoxyribonucleotides. The terms shall also include polynucleosides (i.e., a polynucleotide minus the phosphate) and any other organic base-containing polymer. The terms "nucleic acid" and "oligonucleotide" also encompass nucleic acids or oligonucleotides with a covalently modified base and/or sugar. For example, they include nucleic acids having backbone sugars which are covalently attached to low molecular weight organic groups other than a hydroxyl group at the 2' position and other than a phosphate group at the 5' position. Thus modified nucleic acids may include a 2'-O-alkylated ribose group. In addition, modified nucleic acids may include sugars such as arabinose instead of ribose. Thus the nucleic acids may be heterogeneous in backbone composition thereby containing any possible combination of polymer units linked together such as peptide-nucleic acids (which have amino acid backbone with nucleic acid bases). In some embodiments the nucleic acids are homogeneous in backbone composition.

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The substituted purines and pyrimidines of the immunostimulatory nucleic acids 15 include standard purines and pyrimidines such as cytosine as well as base analogs such as C-5 propyne substituted bases. Wagner RW et al. (1996) Nat Biotechnol 14:840-4. Purines and pyrimidines include but are not limited to adenine, cytosine, guanine, thymine, 5methylcytosine, 2-aminopurine, 2-amino-6-chloropurine, 2,6-diaminopurine, hypoxanthine, and other naturally and non-naturally occurring nucleobases, substituted and unsubstituted aromatic moieties.

The immunostimulatory nucleic acid is a linked polymer of bases or nucleotides. As used herein with respect to linked units of a nucleic acid, "linked" or "linkage" means two entities are bound to one another by any physicochemical means. Any linkage known to those of ordinary skill in the art, covalent or non-covalent, is embraced. Such linkages are well known to those of ordinary skill in the art. Natural linkages, which are those ordinarily found in nature connecting the individual units of a nucleic acid, are most common. The individual units of a nucleic acid may be linked, however, by synthetic or modified linkages.

Whenever a nucleic acid is represented by a sequence of letters it will be understood that the nucleotides are in 5' to 3' (or equivalent) order from left to right and that "A" denotes adenine, "C" denotes cytosine, "G" denotes guanine, "T" denotes thymidine, and "U" denotes uracil unless otherwise noted.

Immunostimulatory nucleic acid molecules useful according to the invention can be obtained from natural nucleic acid sources (e.g., genomic nuclear or mitochondrial DNA or cDNA), or are synthetic (e.g., produced by oligonucleotide synthesis). Nucleic acids isolated from existing nucleic acid sources are referred to herein as native, natural, or isolated nucleic acids. The nucleic acids useful according to the invention may be isolated from any source, including eukaryotic sources, prokaryotic sources, nuclear DNA, mitochondrial DNA, etc. Thus, the term nucleic acid encompasses both synthetic and isolated nucleic acids.

The immunostimulatory nucleic acids can be produced on a large scale in plasmids, (see *Molecular Cloning: A Laboratory Manual*, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1989) and separated into smaller pieces or administered whole. After being administered to a subject the plasmid can be degraded into oligonucleotides. One skilled in the art can purify viral, bacterial, eukaryotic, etc. nucleic acids using standard techniques, such as those employing restriction enzymes, exonucleases or endonucleases.

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For use in the instant invention, the immunostimulatory nucleic acids can be synthesized de novo using any of a number of procedures well known in the art. For example, the Becyanoethyle phosphoramidite method (Beaucage SL and Caruthers MH, Fetrahedron Let 22:1859 (1981)); nucleoside H-phosphonate method (Garegg et al., Fetrahedron Let 27:4051-4054 (1986); Froehler et al., Nucl Acid Res 14:5399-5407 (1986); Garegge et al., Tetrahedron Let 27:4055-4058 (1986); Gaffney et al., Tetrahedron Let 29:2619-2622 (1988)). These chemistries can be performed by a variety of automated oligonucleotide synthesizers available in the market.

The immunostimulatory nucleic acid may be any size of at least 6 nucleotides but in some embodiments are in the range of between 6 and 100 or in some embodiments between 8 and 35 nucleotides in size. Immunostimulatory nucleic acids can be produced on a large scale in plasmids. These may be administered in plasmid form or alternatively they can be degraded into oligonucleotides before administration.

A "stabilized immunostimulatory nucleic acid" shall mean a nucleic acid molecule that is relatively resistant to *in vivo* degradation (e.g., via an exo- or endo-nuclease). Stabilization can be a function of length or secondary structure. Nucleic acids that are tens to hundreds of kbs long are relatively resistant to *in vivo* degradation. For shorter nucleic acids, secondary structure can stabilize and increase their effect. For example, if the 3' end of an

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oligonucleotide has self-complementarity to an upstream region, so that it can fold back and form a sort of stem loop structure, then the oligonucleotide becomes stabilized and therefore exhibits more activity.

Some stabilized immunostimulatory nucleic acids have a modified backbone. It has been demonstrated that modification of the oligonucleotide backbone provides enhanced activity of the immunostimulatory nucleic acids when administered in vivo. Nucleic acids, including at least two phosphorothioate linkages at the 5' end of the oligonucleotide and multiple phosphorothioate linkages at the 3' end, preferably 5, may provide maximal activity and protect the oligonucleotide from degradation by intracelfular exo- and endo-nucleases. Other modified oligonucleotides include phosphodiester modified oligonucleotide, combinations of phosphodiester and phosphorothioate oligonucleotide, methylphosphonate, methylphosphorothioate, phosphorodithioate, and combinations thereof. Each of these combinations and their particular effects on immune cells is discussed in more detail in U.S. Pat. Nos. 6,194,388 and 6,207,646, the entire contents of which are incorporated herein by reference. It is believed that these modified oligonucleotides may show more stimulatory activity due to enhanced nuclease resistance, increased cellular uptake, increased protein binding, and/or altered intracellular localization. Both phosphorothioate and phosphodiester nucleic acids are active in immune cells.

Other stabilized immunostimulatory nucleic acids include: nonionic DNA analogs, such as alkyl- and aryl-phosphates (in which the charged phosphonate oxygen is replaced by an alkyl or aryl group), phosphodiester and alkylphosphotriesters, in which the charged oxygen moiety is alkylated. Oligonucleotides which contain diol, such as tetraethyleneglycol or hexaethyleneglycol, at either or both termini have also been shown to be substantially resistant to nuclease degradation.

Phosphorothioate nucleic acid molecules may be synthesized using automated techniques employing either phosphoramidate or H-phosphonate chemistries. Aryl- and alkyl-phosphonates can be made, e.g., as described in U.S. Pat. No. 4,469,863; and alkylphosphotriesters (in which the charged oxygen moiety is alkylated as described in U.S. Pat. No. 5,023,243 and European Patent No. 092,574) can be prepared by automated solid phase synthesis using commercially available reagents. Methods for making other DNA backbone modifications and substitutions have been described. Uhlmann E and Peyman A (1990) Chem Rev 90:544; Goodchild J (1990) Bioconjugate Chem 1:165.

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Other sources of immunostimulatory nucleic acids useful according to the invention include standard viral and bacterial vectors, many of which are commercially available. In its broadest sense, a "vector" is any nucleic acid material which is ordinarily used to deliver and facilitate the transfer of nucleic acids to cells. The vector as used herein may be an empty vector or a vector carrying a gene which can be expressed. In the case when the vector is carrying a gene the vector generally transports the gene to the target cells with reduced degradation relative to the extent of degradation that would result in the absence of the vector. In this case the vector optionally includes gene expression sequences to enhance expression of the gene in target cells such as immune cells, but it is not required that the gene be expressed in the cell.

Nucleic acid-binding fragments of TLRs are believed to include the extracytoplasmic (extracellular) domain or subportions thereof, such as those which include at least an MBD motif, a CXXC motif, or both an MBD motif and a CXXC motif.

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Both mouse and human TLR9 have an N-terminal extension of approximately 180

amino acids compared to other TLRs. An insertion also occurs at amino acids 253-268,
which is not found in TLRs 1-6 but is present in human TLR7 and human TLR8. This insert

has two CXXC motifs which participate in forming a CXXC domain. The CXXC domain
resembles a zinc finger motif and is found in DNA-binding proteins and in certain specific
CpC binding proteins; e.g., methyl-CpG binding protein-1 (MBD-1). Fujita N et al. (2000)

Mol Cell Biol 20:5107-18. Both human and mouse TLR9 CXXC domains occur at aa 253-268:

CXXC motif:	GNCXXCXXXXXXCXXC	SEQ ID NO:62
Human TLR9:	GNCRRCDHAPNPCMEC	SEQ ID NO:63
Murine TLR9:	GNCRRCDHAPNPCMIC	SEO ID NO:64

An additional motif believed to be involved in CpG binding is the MBD motif, also found in MBD-1, listed below as SEQ ID NO:53. Fujita, N et al.(2000) *Mol Cell Biol* 20:5107-18; Ohki I et al. (1999) *EMBO J* 18:6653-61. Amino acids 524-554 of hTLR9 and aa 525-555 of mTLR9 correspond to the MBD motif of MBD-1 as shown:

MBD motif:

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MBD-1	R-XXXXXXX-R-X-D-X-Y-XXXXXXXXXX-R-S-XXXXXXX-Y	SEQ ID NO:65
hTLR9	Q-XXXXXXX-K-X-D-X-Y-XXXXXXXXX-R-L-XXXXXX-Y	SEQ ID NO:66
mTLR9	O-XXXXXX-K-X-D-X-X-XXXXXXXXX-O-T-XXXXXX-A	SEQ ID NO:67
hTLR9	Q-VLDLSRN-K-L-D-L-Y-HEHSFTELP-R-L-EALDLS-Y	SEQ ID NO:68
mTLR9	Q-VLDLSHN-K-L-D-L-Y-HWKSFSELP-Q-L-QALDLS-Y	SEQ ID NO:69

Although the signaling functions of MBD-1 and TLR9 are quite different, the core D-X-Y is conserved and is believed to be involved in CpG binding.

According to another aspect of the invention, a screening method is provided for identifying an immunostimulatory compound. The method according to this aspect of the invention involves contacting a functional TLR9 with a test compound; detecting presence or absence of a response mediated by a TLR9 signal transduction pathway in the presence of the test compound arising as a result of an interaction between the functional TLR9 and the test compound; and determining the test compound is an immunostimulatory compound when the presence of a response mediated by the TLR9 signal transduction pathway is detected.

An immunostimulatory compound is a natural or synthetic compound that is capable of inducing an immune response when contacted with an immune cell. A TLR9 ligand that is an immunostimulatory compound is a natural or synthetic compound that is capable of inducing an immune response when contacted with an immune cell that expresses TLR9. A TLR9 ligand that is an immunostimulatory compound is also a natural or synthetic compound that is capable of inducing a TLR/IL-1R signal transduction pathway when contacted with a TLR9. Immunostimulatory compounds include but are not limited to immunostimulatory nucleic acids. The immunostimulatory compound can be, for example, a nucleic acid molecule, polynucleotide or oligonucleotide, a polypeptide or oligopeptide, a lipid or lipopolysaccharide, a small molecule.

A basis for certain of the screening assays is the presence of a functional TLR9 in a cell. The functional TLR9 in some instances is naturally expressed by a cell. In other instances, expression of the functional TLR9 can involve introduction or reconstitution of a species-specific TLR9 into a cell or cell line that otherwise lacks the TLR9 or lacks responsiveness to immunostimulatory nucleic acid, resulting in a cell or cell line capable of activating the TLR/IL-1R signaling pathway in response to contact with an

immunostimulatory nucleic acid. In yet other instances, expression of the functional TLR9 can involve introduction of a chimeric or modified TLR9 into a cell or cell line that otherwise lacks the TLR9 or lacks responsiveness to immunostimulatory nucleic acid, resulting in a cell or cell line capable of activating the TLR/IL-1R signaling pathway in response to contact with an immunostimulatory nucleic acid. Examples of cell lines lacking TLR9 or immunostimulatory nucleic acid responsiveness include, but are not limited to, 293 fibroblasts (ATCC CRL-1573), MonoMac-6, THP-1, U937, CHO, and any TLR9 knock-out. The introduction of the species-specific, chimeric or modified TLR9 into the cell or cell line is preferably accomplished by transient or stable transfection of the cell or cell line with a TLR9-encoding nucleic acid sequence operatively linked to a gene expression sequence (as described above). Methods for transient and for stable transfection of a cell are well known in the art.

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The screening assays can have any of a number of possible readout systems based upon either TLR/IL-1R signaling pathway or other assays useful for assessing response to 15 immunostimulatory nucleic acids. It has been reported that immune cell activation by CpG immunostimulatory:sequences is dependent in some way on endosomal processing. Incertain embodiments, the readout for the screening assay is based on the use of \*\*native genesion, alternatively, cotransfected or otherwise co-introduced reporter gene constructs which are responsive to the TLR/IL-1R signal transduction pathway involving 20 MyD88, TRAF; p38, and/or ERK. Häcker H et al. (1999) EMBO J 18:6973-6982. These pathways activate kinases including kB kinase complex and c-Jun N-terminal kinases. Thus reporter genes and reporter gene constructs particularly useful for the assays can include a reporter gene operatively linked to a promoter sensitive to NF-κB. Examples of such promoters include, without limitation, those for NF-κB, IL-1β, IL-6, IL-8, IL-12 p40, CD80, 25 CD86, and TNF-α. The reporter gene operatively linked to the TLR-sensitive promoter can include, without limitation, an enzyme (e.g., luciferase, alkaline phosphatase, β-galactosidase, chloramphenicol acetyltransferase (CAT), etc.), a bioluminescence marker (e.g., greenfluorescent protein (GFP, U.S. Pat. No. 5,491,084), blue fluorescent protein, etc.), a surfaceexpressed molecule (e.g., CD25), and a secreted molecule (e.g., IL-8, IL-12 p40, TNF-α). In certain embodiments the reporter is selected from IL-8, TNF- $\alpha$ , NF- $\kappa$ B-luciferase (NF- $\kappa$ B-30 luc; Häcker H et al. (1999) EMBO J 18:6973-6982), IL-12 p40-luc (Murphy TL et al. (1995)

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Mol Cell Biol 15:5258-5267), and TNF-luc (Häcker H et al. (1999) EMBO J 18:6973-6982). At least one of these reporter constructs (NF-kB-luc) is commercially available (Stratagene, La Jolla, CA). In assays relying on enzyme activity readout, substrate can be supplied as part of the assay, and detection can involve measurement of chemiluminescence, fluorescence, color development, incorporation of radioactive label, drug resistance, or other marker of enzyme activity. For assays relying on surface expression of a molecule, detection can be accomplished using FACS analysis or functional assays. Secreted molecules can be assayed using enzyme-linked immunosorbent assay (ELISA) or bioassays. Many such readout systems are well known in the art and are commercially available.

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According to one embodiment of this method, comparison can be made to a reference immunostimulatory nucleic acid. The reference immunostimulatory nucleic acid may be any suitably selected immunostimulatory nucleic acid, including a CpG nucleic acid. In certain embodiments the screening method is performed using a plurality of test nucleic acids. In certain embodiments comparison of test and reference responses is based on comparison of quantitative measurements of responses in each instance.

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In another aspect the invention provides a screening method for identifying species specificity of an immunostimulatory nucleic acid. The method involves contacting a TLR9 of a first species with a test immunostimulatory nucleic acid; contacting a TLR9 of a second species with the test immunostimulatory nucleic acid; measuring a response mediated by a TLR signal transduction pathway associated with the contacting the TLR9 of the first species with the test immunostimulatory nucleic acid; measuring a response mediated by the TLR signal transduction pathway associated with the contacting the TLR9 of the second species with the test immunostimulatory nucleic acid; and comparing the two responses. The TLR9 may be expressed by a cell or it may be part of a cell-free system. The TLR9 may be part of a complex, with either another TLR or with another protein, e.g., MyD88, IRAK, TRAF, IκB, NF-κB, or functional homologues and derivatives thereof. Thus for example a given ODN can be tested against a panel of human fibroblast 293 fibroblast cells transfected with TLR9 from various species and optionally cotransfected with a reporter construct sensitive to TLR/IL-1R activation pathways. Thus in another aspect, the invention provides a method for screening species selectivity with respect to a given nucleic acid sequence.

> Test compounds can include but are not limited to peptide nucleic acids (PNAs), antibodies, polypeptides, carbohydrates, lipids, hormones, and small molecules. Test

compounds can further include variants of a reference immunostimulatory nucleic acid incorporating any one or combination of the substitutions described above. Test compounds can be generated as members of a combinatorial library of compounds.

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In preferred embodiments, the screening methods can be performed on a large scale and with high throughput by incorporating, e.g., an array-based assay system and at least one automated or semi-automated step. For example, the assays can be set up using multiple-well plates in which cells are dispensed in individual wells and reagents are added in a systematic manner using a multiwell delivery device suited to the geometry of the multiwell plate. Manual and robotic multiwell delivery devices suitable for use in a high throughput screening assay are well known by those skilled in the art. Each well or array element can be mapped in a one-to-one manner to a particular test condition, such as the test compound. Readouts can also be performed in this multiwell array, preferably using a multiwell plate reader device or the like. Examples of such devices are well known in the art and are available through commercial sources. Sample and reagent handling can be automated to further enhance the 15 sthroughput capacity of the screening assay, such that dozens, hundreds, thousands, or even millions of parallel assays can be performed in a day or in a week. Fully robotic systems are with how many the rarte for applications such as generation and analysis of combinatorial libraries of synthetic compounds. See, for example, U.S. Pat. Nos. 5,443,791 and 5,708,158.

The following examples are provided for illustrative purposes and are not meant to be 20 limiting in any way.

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## **Examples**

Example 1. Cloning and Sequencing of Rat, Porcine, Bovine, Equine, Ovine, Canine, and 25 Feline TLR9

Cells and Tissues. Lymphoid tissues, primarily spleen or blood mononuclear cells (PBMC) from five mammalian species were collected: mouse, pig, bovine, rat and horse. Spleen samples were collected in RNAlater<sup>TM</sup> (Ambion<sup>®</sup>, Austin, TX, USA), stabilized at 4°C overnight and stored at -70°C. Blood samples were centrifuged at 500 x g for 25 min at room temperature and the buffy coat, containing enriched PBMC, was then removed and stored at -70°C. The mouse specimen was used as a comparative positive control.

First-strand cDNA synthesis. Total RNA from the spleen and PBMC samples was isolated using a monophasic solution of phenol and guanidine isothiocyanate: TRIzol<sup>TM</sup> reagent (GIBCO BRL<sup>®</sup>, Burlington, ON, Canada) according to the manufacturer's instructions: First-strand cDNA was synthesized from the total RNA using SUPERSCRIPT<sup>TM</sup> II reverse transcriptase (GIBCO BRL<sup>®</sup>, Burlington, ON, Canada). Approximately 3 μg of total RNA was added to 50 pmoles of oligo(dT) primer [poly T<sub>(18)</sub>]; the mixture was heated to 70°C for 10 min and subsequently chilled on ice. The following was added to the cooled reaction mixture: 1 μl of mixed dNTP stock containing 10 mM each dATP, dCTP, dGTP and dTTP (Amersham Pharmacia Biotech Inc., Baie de Urfe, Quebec) at neutral pH, 1X first strand buffer (50 mM Tris-HCl pH 8.3/75 mM KCl/3 mM MgCl<sub>2</sub>) and 2 μl of 0.1 M DTT. The mixture was subsequently heated to 42°C for 2 min, followed by addition of 200 units of SUPERSCRIPT<sup>TM</sup> II reverse transcriptase. The reaction was carried out at 42°C for 50 min, followed by 70°C for 15 min. The first-strand cDNA was used as the template for subsequent polymerase chain reaction (PCR) amplifications.

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PCR amplification. TLR9 gene was PCR amplified from each of the above-mentioned species using primers designed from known mouse and human TLR9 sequence in Genbank: Accession AF314224 and AF259262, respectively. The primers were designed using the primer design software, Clone Manager 5 (Scientific and Educational Software, Durham, NC, USA). TLR9 gene-specific primers used were: forward primer 5'-ACCTTGCCTGCCTTCCTACCCTGTGA-3' (SEQ ID NO:37) and reverse primer 5'-GTCCGTGTGGGCCAGCACAAA-3' (SEQ ID NO:38).

The 2.7 Kbp fragment was PCR amplified using Advantage® 2 DNA polymerase mix (BD Biosciences Clontech, Palo Alto, CA, USA) according to the manufacturer's instructions. PCR reaction volumes of 25 μl contained 15 pmoles of each primer, 0.2 mM of dNTP mix and 1 μl of reverse transcription reaction. PCR amplification was conducted by initial denaturation at 94°C for 1 min followed by 30 cycles of 94°C denaturation (15 sec), 65°C annealing (45 sec) and 72°C extensions (2 min), with a final extension at 72°C for 5 min.

Cloning and sequencing. The PCR amplified fragment was treated with 500 units of T4 DNA polymerase (Amersham Pharmacia Biotech Inc., Baie de Urfe, Quebec) for 15 min at room temperature prior to cleaning the reaction with QIAquick PCR purification kit (QIAGEN Inc., Mississauga, ON, Canada). The fragment was then ligated to pZErO™ - 2

vector (Invitrogen<sup>™</sup> Life Technologies, Burlington, ON, Canada), treated with *Eco RV* restriction enzyme, using T4 DNA Ligase (GIBCO BRL<sup>®</sup>, Burlington, ON, Canada). *E. coli* TOP 10 chemically competent cells (Invitrogen<sup>™</sup> Life Technologies, Burlington, ON, Canada) were used to transform ligated products. Plasmids containing the 2.7 Kbp fragment were sequenced using an automated DNA sequencer, CEQ<sup>™</sup> 2000XL DNA analysis system (Beckman Coulter Inc., Fullerton, CA, USA).

Sequences of the 2.7 Kbp fragment were derived from three clones of each species selected from independent PCR reactions to account for errors that may have been incurred during the PCR amplifications and to confirm the sequence data.

Nucleotide sequences of the rat, porcine, bovine, equine, ovine, canine, and feline TLR9 were extended and completed using standard 5' and 3' RACE PCR and primers designed using the sequences obtained from the 2.7 Kbp fragments.

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Results. Nucleotide sequences of rat, porcine, bovine, equine, canine, and feline TLR9 cDNA obtained by the methods above are provided as SEQ ID NOs 3, 7, 11, 15, 19, 23, and 27, respectively. Deduced amino acid sequences are provided as SEQ ID NOs 1, 5, 9, 13, 17, 21, and 25, respectively. Deduced amino acid sequences of full-length murine and whuman TER9 are provided as SEQ ID NOs 29 and 33, respectively.

Example 2: Comparison of Aligned Sequences for TLR9 from Various Mammalian Species.

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bovine, mouse, ovine, porcine, horse, human, and rat TLR9 polypeptides was performed using Clustal W 1.82 (see, for example, www.cmbi.kun.nl/bioinf/tools/clustalw.shtml). In addition, paired sequence alignment of deduced amino acid sequences for murine and human TLR9 polypeptides was performed using Clustal W 1.82. The results of the multiple sequence alignment are presented in Figure 1. As will be appreciated from Figure 1, certain amino acids are highly conserved across all species examined. Similarly, certain amino acids differ only by conservative amino acid substitutions among the various species. In addition, it is evident that certain amino acids which are conserved between murine and human TLR9 are not conserved in other species. Furthermore, Figure 1 also indicates that certain amino acids are highly divergent across various species. The information provided by the comparison of multiple species adds significantly to the information available by comparison between only murine and human TLR9 sequences.

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The putative transmembrane regions of the TLR9 polypeptides are indicated in boxes in Figure 1. Sequence upstream of each transmembrane region is extracellular domain and is believed to include sequence primarily responsible for binding to TLR9 ligands, including CpG DNA. The extracellular domains of feline, canine, bovine, mouse, ovine, porcine, horse, human, and rat TLR9 correspond to amino acids numbered 1-820, 1-822, 1-818, 1-821, 1-818, 1-819, 1-820, 1-820, and 1-821, respectively, as shown in Figure 1.

Figure 2 presents an evolutionary relatedness tree for six TLR9 polypeptides examined. The cladogram in Figure 2 was prepared using Clustal W (see above). As can be appreciated from this figure, murine and human TLR9 are nearly the most divergent TLR9s in this group. Surprisingly, human and horse TLR9 appear relatively closely related.

Example 3. Reconstitution of TLR9 Signaling in 293 Fibroblasts.

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Mouse TLR9 cDNA (SEQ ID NO:31) and human TLR9 cDNA (SEQ ID NO:35) in pT-Adv vector (from Clonetech) were individually cloned into the expression vector pcDNA3.1(-) from Invitrogen using the EcoRI site. Utilizing a "gain of function" assay it was possible to reconstitute human TLR9 (hTLR9) and murine TLR9 (mTLR9) signaling in CpG-DNA non-responsive human 293 fibroblasts (ATCC, CRL-1573). The expression vectors mentioned above were transfected into 293 fibroblast cells using the calcium phosphate method.

Since NF-κB activation is central to the IL-1/TLR signal transduction pathway (Medzhitov R et al. (1998) *Mol Cell* 2:253-258; Muzio M et al. (1998) *J Exp Med* 187:2097-101), cells were transfected with hTLR9 or co-transfected with hTLR9 and an NF-κB-driven luciferase reporter construct. Human fibroblast 293 cells were transiently transfected with hTLR9 and a six-times NF-κB-luciferase reporter plasmid (NF-κB-luc) or with hTLR9 alone. After stimulus with CpG-ODN (2006, 2μM, TCGTCGTTTTGTCGTTTTGTCGTT, SEQ ID NO:58), GpC-ODN (2006-GC, 2μM, TGCTGCTTTTGTGCTTTTGTGCTT, SEQ ID NO:59), LPS (100 ng/ml) or media, NF-κB activation by luciferase readout (8h) or IL-8 production by ELISA (48h) were monitored. Results representative of three independent experiments showed that cells expressing hTLR9 responded to CpG-DNA but not to LPS.

Independently, human fibroblast 293 cells were transiently transfected with mTLR9 and the NF-κB-luc construct or with mTLR9 alone. After stimulation with CpG-ODN (1668, 2μM; TCCATGACGTTCCTGATGCT, SEQ ID NO:60), GpC-ODN (1668-GC, 2μM;

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TCCATGAGCTTCCTGATGCT, SEQ ID NO:61), LPS (100 ng/ml) or media, NF-kB activation by luciferase readout (8h) or IL-8 production by ELISA (48h) were monitored. Results showed that expression of TLR9 (human or mouse) in 293 cells results in a gain of function for CpG-DNA stimulation.

To generate stable clones expressing human TLR9, murine TLR9, or either TLR9 with the NF-κB-luc reporter plasmid, 293 cells were transfected in 10 cm plates (2x10<sup>6</sup> cells/plate) with 16 μg of DNA and selected with 0.7 mg/ml G418 (PAA Laboratories GmbH, Cölbe, Germany). Clones were tested for TLR9 expression by RT-PCR. The clones were also screened for IL-8 production or NF-κB-luciferase activity after stimulation with ODN. Four different types of clones were generated.

293-hTLR9-luc:

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expressing human TLR9 and 6-fold NF-κB-luciferase reporter

293-mTLR9-luc:

expressing murine TLR9 and 6-fold NF-kB-luciferase reporter

293-hTLR9:

expressing human TLR9

293-mTLR9:

\*\*rexpressing murine TLR9

Results indicated that stable clones also responded to CpG-ODN.

Example 4. Similar ODN Sequence Specificity of TLR9 of Human and Equine TLR9.

3x10<sup>6</sup>·293T cells were electroporated with 5μg NF-κB-luc plasmid and 5 μg of either horse TLR9-pcDNA3.1 plasmid or humanTLR9-pcDNA3.1 plasmid at 200V, 975 μF. After the electroporation the cells were plated in 96-well cell culture plates at 2.5x10<sup>4</sup> cells per well and grown overnight at 37°C. The cells were stimulated with the indicated concentration of ODN for 16h, after which the supernatant was removed and the cells lysed in lysis buffer and frozen for at least 2 hours at –80°C. Luciferase activity was measured by adding Luciferase Assay substrate from Promega. Values are given as fold specific induction over non-stimulated control. Results are shown in Figure 3.

As shown in Figure 3, ODN 2006 (TCGTCGTTTTGTCGTTTTGTCGTT; SEQ ID NO:58) has a strong specificity for human TLR9. ODN 1982

(TCCAGGACTTCTCAGGTT; SEQ ID NO:70) was the negative control ODN. ODN 5890 (TCCATGACGTTTTTGATGTT; SEQ ID NO:39) has a strong specificity for mouse

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TLR9. This experiment demonstrates the similarity of horse TLR9 to human TLR9 in binding specificity, a result predicted by the evolutionary relatedness of horse TLR9 to human TLR9. Mouse TLR9 is more distant from horse TLR9 and human TLR9 in sequence homology, and ODN 5890 was not detected by either human or horse TLR9.

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Example 5. Non-human, Non-murine Native Mammalian TLR9 Useful in Screening for Human-Preferred CpG DNA.

Native rat, porcine, bovine, equine, and ovine TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006). Rat, porcine, bovine, equine, or ovine TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in this assay are then used as the basis for screening for additional human-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected native rat, porcine, bovine, equine, or ovine TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected native rat, porcine, bovine, equine, or ovine TLR9 polypeptide are contacted with candidate human-preferred CpG DNA. Candidate human-preferred CpG DNA candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA.

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Example 6. Chimeric TLR9 Useful in Screening for Human-Preferred CpG DNA.

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Chimeric TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006). Chimeric TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in this assay are then used as the basis for screening for additional human-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected chimeric TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected chimeric TLR9 polypeptide are contacted with candidate human-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA.

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Example 7. Chimeric TLR9 Responsive to Both Human-Preferred and Murine-Preferred CpG DNA.

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Chimeric TLR9 polypeptides are screened for binding or TLR9 signaling activity when contacted with human-preferred CpG DNA (ODN 2006) and also screened for binding or TLR9 signaling activity when contacted with murine-preferred CpG DNA (ODN 1668). Chimeric TLR9 polypeptides which exhibit significant TLR9 binding or TLR9 signaling activity in each of these assays are then used as the basis for screening for additional human-preferred CpG DNA and for screening for additional murine-preferred CpG DNA. An expression vector containing a nucleic acid sequence encoding a selected chimeric TLR9 polypeptide, and optionally a reporter construct, is introduced into cells which do not express TLR9. The cells expressing the selected chimeric TLR9 polypeptide are contacted with candidate human-preferred CpG DNA or candidate murine-preferred CpG DNA. Candidate human-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as human-preferred CpG DNA. Candidate murine-preferred CpG DNA exhibiting significant TLR9 binding or TLR9 signaling activity are selected as murine-preferred CpG DNA.

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The foregoing written specification is considered to be sufficient to enable one skilled winthe artito practice the invention. The present invention is not to be limited in scope by examples provided, since the examples are intended as a single illustration of one aspect of the invention and other functionally equivalent embodiments are within the scope of the invention. Various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims. The advantages of the invention are not necessarily encompassed by each embodiment of the invention.

All references, patents and patent publications that are recited in this application are incorporated in their entirety herein by reference.

We claim:

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## Claims

- 1. An isolated polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:1, SEQ ID NO:5, SEQ ID NO:9, SEQ ID NO:13, and SEQ ID NO:17.
- 2. An isolated polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, and SEQ ID NO:18.
- An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a
   polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:1, SEQ
   ID NO:5, SEQ ID NO:9, SEQ ID NO:13, and SEQ ID NO:17.
  - 4. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide comprising an amino acid sequence selected from the group SEQ ID NO:2, SEQ ID NO:6, SEQ ID NO:10, SEQ ID NO:14, and SEQ ID NO:18.
    - 5. A vector comprising the nucleic acid of any of claims 3-4.
    - 6. A cell comprising the vector of claim 5.
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  - 7. An antibody or fragment thereof that binds specifically to the polypeptide of any of claims 1-2.
  - 8. A method for identifying key amino acids in a TLR9 of a first species which confer specificity for CpG DNA optimized for TLR9 of the first species, comprising:

aligning protein sequences of TLR9 of a first species, TLR9 of a second species, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for TLR9 of the first species rather than when contacted with a CpG DNA optimized for TLR9 of the second species;

generating an initial set of candidate amino acids in the TLR9 of the first species by excluding each amino acid in the TLR9 of the first species which (a) is identical with the

TLR9 of the second species or (b) differs from the TLR9 of the second species only by conservative amino acid substitution;

generating a refined set of candidate amino acids by selecting each amino acid in the initial set of candidate amino acids in the TLR9 of the first species which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and

identifying as key amino acids in the TLR9 of the first species each amino acid in the refined set of candidate amino acids.

9. A method for identifying key amino acids in human TLR9 which confer specificity for CpG DNA optimized for human TLR9, comprising:

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aligning protein sequences of human TLR9, murine TLR9, and TLR9 of a third species, wherein the TLR9 of the third species preferentially generates a signal when contacted with a CpG DNA optimized for human TLR9 rather than when contacted with a CpG DNA optimized for murine TLR9;

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\*generating an initial set of candidate amino acids in human TLR9 by excluding each amino acids in human TLR9 which (a) is identical with murine TLR9 or (b) differs from amurine TER9 only by conservative amino acid substitution;

generating a refined set of candidate amino acids by selecting each amino acid in the initialiset of candidate amino acids in human TLR9 which (a) is identical with the TLR9 of the third species or (b) differs from the TLR9 of the third species only by conservative amino acid substitution; and

identifying as key amino acids in human TLR9 each amino acid in the refined set of candidate amino acids.

10. The method according to claim 9, performed iteratively with a plurality of TLR9s derived from different species other than human and mouse, wherein for each TLR9 the refined set of candidate amino acids is assigned a weight, said weight corresponding to a ratio equal to (responsiveness to human-preferred CpG DNA)/(responsiveness to murine-preferred CpG DNA).

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- 11. An isolated polypeptide comprising an amino acid sequence identical to SEQ ID NO:30 except for substitution of at least one key amino acid identified according to the method of any of claims 9 or 10.
- 5 12. An isolated nucleic acid molecule comprising a nucleic acid sequence encoding a polypeptide according to claim 11.
  - 13. A vector comprising the nucleic acid of claim 12.
- 10 14. A cell comprising the vector of claim 13.
  - 15. An antibody that binds specifically to the polypeptide of claim 14.
  - 16. A screening method to identify a TLR9 ligand, comprising: contacting a polypeptide according to any of claims 1, 2, or 11 with a candidate TLR9 ligand;

measuring a signal in response to the contacting; and identifying the candidate TLR9 ligand as a TLR9 ligand when the signal in response to the contacting is consistent with TLR9 signaling.

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- 17. The method of claim 16, wherein the signal comprises expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway.
- 18. The method of claim 17, wherein the reporter gene is operatively linked to a promoter sensitive to NF-κB.
  - 19. The method of claim 17, wherein the candidate TLR9 ligand is an immunostimulatory nucleic acid.
- 20. The method of claim 19, wherein the immunostimulatory nucleic acid is CpG DNA.

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21. A screening method to identify species-specific CpG-motif preference of an isolated polypeptide of claim 2 or claim 11, comprising:

contacting an isolated polypeptide of claim 2 or claim 11 with a CpG DNA comprising a hexamer sequence selected from the group consisting of GACGTT, AACGTT, CACGTT, TACGTT, GGCGTT, GCCGTT, GTCGTT, GATGTT, GAAGTT, GAGGTT, GACATT, GACCTT, GACGTT, G

measuring a signal in response to the contacting; and identifying a species-specific CpG-motif preference when the signal in response to the contacting is consistent with TLR9 signaling.

- 22. The method of claim 21, wherein the signal comprises expression of a reporter gene responsive to TLR/IL-1R signal transduction pathway.
- 23. The method of claim 17, wherein the reporter gene is operatively linked to a promoter sensitive to NF-kB.

having a sequence selected from the group consisting of

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(SEO ID NO:39),
        *TCCATGACGTTTTTGATGTT
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        .TCCATAACGTTTTTGATGTT
                                    (SEQ ID NO:40),
                                    (SEQ ID NO:41),
         TCCATCACGTTTTTGATGTT
                                    (SEQ ID NO:42),
         TCCATTACGTTTTTGATGTT
                                    (SEQ ID NO:43),
         TCCATGGCGTTTTTGATGTT
                                    (SEQ ID NO:44),
         TCCATGCCGTTTTTGATGTT
25
                                    (SEQ ID NO:45),
         TCCATGTCGTTTTTGATGTT
                                    (SEQ ID NO:46),
         TCCATGATGTTTTTGATGTT
                                    (SEQ ID NO:47),
         TCCATGAAGTTTTTGATGTT
         TCCATGAGGTTTTTGATGTT
                                    (SEQ ID NO:48),
                                    (SEQ ID NO:49),
         TCCATGACATTTTTGATGTT
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                                    (SEQ ID NO:50),
         TCCATGACCTTTTTGATGTT
         TCCATGACTTTTTTGATGTT
                                    (SEQ ID NO:51),
         TCCATGACGCTTTTGATGTT
                                    (SEQ ID NO:52),
                                    (SEO ID NO:53),
         TCCATGACGATTTTGATGTT
                                    (SEQ ID NO:54),
         TCCATGACGGTTTTGATGTT
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                                    (SEQ ID NO:55),
         TCCATGACGTCTTTGATGTT
         TCCATGACGTATTTGATGTT
                                    (SEO ID NO:56), and
                                    (SEQ ID NO:57).
         TCCATGACGTGTTTGATGTT
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## Figure 1 (1/3)

	feline	MGPCHGALHPLSLLVQAAALAVALAQGTLPAFLPCELQRHGLVNCDWLFLKSVPHFSAAA	60
	canine	MGPCRGALHPLSLLVQAAALALALAQGTLPAFLPCELQPHGLVNCNWLFLKSVPRFSAAA	60
	bovine	MGP-YCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGA	59
	mouse	MGP-YCAPHPLSLLVQAAALAAALAEGTLPAFLPCELQPHGQVDCNWLFLKSVPHFSAGA	59
	ovine	MGP-YCAPHPLSLLVQAAALAAALAQGTLPAFLPCELQPRGKVNCNWLFLKSVPRFSAGA	59
	porcine	MGP-RCTLHPLSLLVQVTALAAALAQGRLPAFLPCELQPHGLVNCNWLFLKSVPHFSAAA	59
	horse	MGPCHGALQPLSLLVQAAMLAVALAQGTLPPFLPCELQPHGLVNCNWLFLKSVPHFSAAA	60
	human	MGFCRSALHPLSLLVQAIMLAMTLALGTLPAFLPCELQPHGLVNCNWLFLKSVPHFSMAA	60
	rat	MVLCRRTLHPLSLLVQAAVLAEALALGTLPAFLPCELKPHGLVDCNWLFLKSVPHFSAAE	60
		* ::******. ** :** * **.****** : * *:*:*******	
	feline	DROWNAY AT VAND THE REAL PROPERTY AND ADDRESS OF THE PROPERTY	
	canine	PRGNVTSLSLYSNRIHLHDSDFVHLSSLRRLNLKWNCPPASLSPMHFPCHMTIEPHTFL	120
	bovine	PRGNVTSLSLYSNRIHHLHDYDFVHFVHLRRLNLKWNCPPASLSPMHFPCHMTIEPNTFL	120
		PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL	
	mouse	PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL	
	ovine	PRANVTSLSLISNRIHHLHDSDFVHLSNLRVLNLKWNCPPAGLSPMHFPCRMTIEPNTFL	119
	porcine	PRANYTSLSLLSNRIHHLHDSDFVHLSSLRTLNLKWNCPPAGLSPMHFPCHMTIEPNTFL	119
	horse	PRDNVTSLSLLSNRIHHLHDSDFAQLSNLQKLNLKWNCPPAGLSPMHFPCHMTIEPNTFL	
	human	PRGNVTSLSLSSNRIHHLHDSDFAHLPSLRHLNLKWNCPPVGLSPMHFPCHMTIEPSTFL	
	rat	PRSNITSLSLIANRIHHLHNLDFVHLPNVRQLNLKWNCPPPGLSPLHFSCRMTIEPKTFL	120
		** *:**** :****** : **.:: :: ******* .**:**.*:***	
	feline	AVPTLEELNLSYNSITTVPALPSSLVSLSLSRTNILVLDPANLAGLHSLRFLFLDGNCYY	100
	canine	AVPTLEDLNLSYNSITTVPALPSSLVSLSLSRTNILVLDPATLAGLYALRFLFLDGNCYY	
	bovine	AVPTLEELNLSYNGITTVPALPSSLVSLSLSHTSILVLGPTHFTGLHALRFLYMDGNCYY	
	mouse	AVPTLEELNLSYNGITTVPALPSSLVSLSSHTSILVLGPTHFTGLHALRFLYMDGNCYY	
	ovine	AVPTLEELNLSYNGITTVPALPSSLVSLSLSRTSILVLGPTHFTGLHALRFLYMDGNCYY	
*		AVPTLEELNLSYNSITTVPALPDSLVSLSLSRTNILVLDPTHLTGLHALRYLYMDGNCYY	
	horse	AVPTLEELNLSYNGITTVPALPSSLVSLILSRTNILQLDPTSLTGLHALRFLYMDGNCYY	
		AVYTEELINLSYNNIMTVPALPKSLISLSLSHTNIIMLDSASLAGLHALRFLFMDGNCYY	
•	rat	AMRMLEELNLSYNGITTVPRLPSSLTNLSLSHTNILVLDASSLAGLHSLRVLFMDGNCYY	
		**************************************	100
	feline www.	KNPGPQALQVAPGALLGLGNLTHLSLKYNNLTAVPRGLPPSLEYLLLSYNHIITLAPEDL	240
	canine	KNPCQQALQVAPGALLGLGNLTHLSLKYNNLTVVPRGLPPSLEYLLLSYNHIITLAPEDL	
		MNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIVTLAPEDL	
• •	mouse	MNPCPRALEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIVTLAPEDL	
•	ovine .	KNPCQQAVEVAPGALLGLGNLTHLSLKYNNLTEVPRRLPPSLDTLLLSYNHIITLAPEDL	
- •	porcine	KNPCQGALEVVPGALLGLGNLTHLSLKYNNLTEVPRSLPPSLETLLLSYNHIVTLTPEDL	
	horse .	KNPCGRALEVAPGALLGLGNLTHLSLKYNNLTTVPRSLPPSLEYLLLSYNHIVTLAPEDL	
•	human	KNPCRQALEVAPGALLGLGNLTHLSLKYNNLTVVPRNLPSSLEYLLLSYNRIVKLAPEDL	
	rat	KNPCNGAVNVTPDAFLGLSNLTHLSLKYNNLTEVPROLPPSLEYLLLSYNLIVKLGAEDL	
		*** *::*.*.*********** *** **.** **** *:.* .**	
	feline	ANLTALRVLDVGGNCRRCDHARNPCMECPKGFPHLHPDTFSHLNHLEGLVLKDSSLYNLN	
	canine	ANLTALRVLDVGGNCRRCDHARNPCRECPKGFPQLHPNTFGHLSHLEGLVLRDSSLYSLD	
	bovine	ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE	
	mouse	ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE	
	ovine	ANLTALRVLDVGGNCRRCDHARNPCRECPKNFPKLHPDTFSHLSRLEGLVLKDSSLYKLE	
	porcine	ANLTALRVLDVGGNCRRCDHARNPCRECPKDHPKLHSDTFSHLSRLEGLVLKDSSLYNLD	
•	horse	ANLTALRVLDVGGNCRRCDHARNPCVECPHKFPQLHSDTFSHLSRLEGLVLKDSSLYQLN	
	human	ANLTALRVLDVGGNCRRCDHAPNPCMECPRHFPQLHPDTFSHLSRLEGLVLKDSSLSWLN	
	rat	ANLTSLRMLDVGGNCRCDHAPDLCTECRQKSLDLHPQTFHHLSHLEGLVLKDSSLHSLN ***:**:*********** : * ** : .**.:** **.:****** *:	300
	feline	${\tt PRWFHALGNLMVLDLSENFLYDCITKTTAFQGLAQLRRLNLSFNYHKKVSFAHLHLAPSF}$	360
	canine	PRWFHGLGNLMVLDLSENFLYDCITKTKAFYGLARLRRLNLSFNYHKKVSFAHLHLASSF	360
	bovine	KDWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSF	359
	mouse	KDWFRGLGRLQVLDLSENFLYDYITKTTIFNDLTQLRRLNLSFNYHKKVSFAHLHLASSF	359
	ovine	KDWFRGLGRLQVLDLSENFLYDYITKTTIFRNLTQLRRLNLSFNYHKKVSFAHLQLAPSF	359
	porcine	TRWFRGLDRLQVLDLSENFLYDCITKTTAFQGLARLRSLNLSFNYHKKVSFAHLHLAPSF	
	horse	PRWFRGLGNLTVLDLSENFLYDCITKTKAFQGLAQLRRLNLSFNYHKKVSFAHLTLAPSF	
	human	ASWFRGLGNLRVLDLSENFLYKCITKTKAFQGLTQLRKLNLSFNYQKRVSFAHLSLAPSF	
	rat	SKWFQGLANLSVLDLSENFLYESINKTSAFQNLTRLRKLDLSFNYCKKVSFARLHLASSF	
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# Figure 1 (2/3)

feline	GSLLSLQQLDMHGIFFRSLSETTLRSLVHLPMLQSLHLQMNFINQAQLSIFGAFPGLRYV 420
canine	GSLLSLOELDIHGIFFRSLSKTTLQSLAHLPMLQRLHLQLNFISQAQLSIFGAFPGLRYV 420
bovine	GSLVSLEKLDMHGIFFRSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFV 419
mouse	GSLVSLEKLDMHGIFFRSLTNITLQSLTRLPKLQSLHLQLNFINQAQLSIFGAFPSLLFV 419
ovine	GGLVSLEKLDMHGIFFRSLTNTTLRPLTQLPKLQSLSLQLNFINQAELSIFGAFPSLLFV 419
porcine	GHLRSLKELDMHGIFFRSLSETTLQPLVQLPMLQTLRLQMNFINQAQLSIFGAFPGLLYV 419
horse	GSLLSLQELDMHGIFFRSLSQKTLQPLARLPMLQRLYLQMNFINQAQLGIFKDFPGLRYI 420
human	GSLVALKELDMHGIFFRSLDETTLRPLARLPMLQTLRLQMNFINQAQLGIFRAFPGLRYV 420
rat	KSLVSLQELNMNGIFFRLLNKNTLRWLAGLPKLHTLHLQMNFINQAQLSVFSTFRALRFV 420
	* :*::*::**** * : **: *. ** *: * **:***.**:* * .* ::
feline	DLSDNRISGAMELAAATGEVDGGERVRLPSGDLALGPPGTPSSEGFMPGCKTLNFTLD 478
canine	DLSDNRISGAAEPAAATGEVEADCGERVWPQSRDLALGPLGTPGSEAFMPSCRTLNFTLD 480
bovine	DLSDNRISGAATPAAALGEVDSRVEVWRLPRGLAPGPLDAVSSKDFMPSCN-LNFTLD 476
mouse	DLSDNRISGAATPAAALGEVDSRVEVWRLPRGLAPGPLDAVSSKDFMPSCN-LNFTLD 476
ovine	DLSDNRISGAARPVAALGEVDSGVEVWRWPRGLAPGPLAAVSAKDFMPSCN-LNFTLD 476
porcine	DLSDNRISGAARPVAITREVDGRERVWLPSRNLAPRPLDTLRSEDFMPNCKAFSFTLD 477
horse	DLSDNRISGAVEPVATTGEVDGGKKVWLTSRDLTPGPLDTPSSEDFMPSCKNLSFTLD 478
human	DLSDNRISGASELTATMGEADGGEKVWLQPGDLAPAPVDTPSSEDFRPNCSTLNFTLD 478
rat	DLSNNRISGPPTLSRVAPEKAD-EAEKGVPWPASLTPALPSTPVSKNFMVRCKNLRFTMD 479
•	***:****
feline	LSRNNLVTIQPEMFARLSRLQCLLLSRNSISQAVNGSQFMPLTSLQVLDLSHNKLDLYHG 538
canine	LSRNNLVTVQPEMFVRLARLQCLGLSHNSISQAVNGSQFVPLSNLRVLDLSHNKLDLYHG 540
bovine	LSRNNLVTIOOEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG 536
mouse	LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG 536
+ovine	LSRNNLVTIQQEMFTRLSRLQCLRLSHNSISQAVNGSQFVPLTRLRVLDLSYNKLDLYHG 536
porcine	LSRNNLVTIOSEMFARLSRLECLRLSHNSISQAVNGSQFVPLTSLRVLDLSHNKLDLYHG 537
horse	LSRNNLVTYQPEMFAQLSRLQCLRLSHNSISQAVNGSQFVPLTSLQVLDLSHNKLDLYHG 538
human	**JLSRNNLVTVQPEMFAQLSHLQCLRLSHNCISQAVNGSQFLPLTGLQVLDLSHNKLDLYHE 538
rat	LSRNNQVTIKPEMFVNLSHLQCLSLSHNCIAQAVNGSQFLPLTNLKVLDLSYNKLDLYHS 539
	# \$##### \##; O.\###; \#; \##\\##\##\######### \##; \#; \
feline	***RSFTELPREALDLSYNSOPESMOGVGHNESFVAQLPALRYLSLAHNDIHSRVSQQLCSA 598
	REFTELPREALDLSYNSOPFSMOGVGHNESFVAQLPALRYLSLAHNDIHSRVSQQLCSA 598  #REFTELPREALDLSYNSOPFSMRGVGHNESFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600
canine	#RSFTELPREALDLSYNSOPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ATRSFTELPOLEALDLSYNSOPFSMOGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596
canine bovine	#.RSFTELPREALDLSYNSOPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ***********************************
canine bovine mouse	#.RSFTELPREALDLSYNSOPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ***********************************
canine bovine mouse ovine	#.RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ATRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #.RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #.RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #.RSFTELPRLEALDLSYNSOPFTMOGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA 597
canine bovine mouse	#.RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ATRSFTELPQEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #.RSFTELPQEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #.RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #.RSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA 597 #.RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598
canine bovine mouse ovine porcine	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600  ATRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCST 598  HSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598
canine bovine mouse ovine porcine horse	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ARSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 RSFTELPRLEALDLSYNSQPFTMQGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA 597 RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598 HSFTELPRLEALDLSYNSQPFGMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 KSFSELPQLOALDLSYNSQPFSMOGIGHNFSFLANLSRLONLSLAHNDIHSRVSSRLYST 599
canine bovine mouse ovine porcine horse human	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600  ATRSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCST 598  HSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598
canine bovine mouse ovine porcine horse human rat	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ARSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 RSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNDIHSRVSQQLCSA 597 RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598 HSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599 :**:**:*::***:*:*:*::*::*::*::*:::*::
canine bovine mouse ovine porcine horse human rat	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ARSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPRIEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNDIHSRVSQKLSSA 596  *RSFTELPRIEALDLSYNSQPFSMQGVGHNLSFVAQLPTLRYLSLAHNDIHSRVSQQLCST 598  *HSFTELPRIEALDLSYNSQPFSMQGVGHNLSFVAQLPTLRYLSLAHNNIHSQVSQQLCST 598  *KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598  *KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599  :**:**:*:::**:::*::::::::::::::::::
canine bovine mouse ovine porcine horse human rat  feline canine	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ARSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPRIEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNDIHSRVSQKLSSA 596  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNDIHSRVSQQLCSA 597  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSA 598  **HSFTELPRIEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598  **KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599  :**:**:*::*::::::::::::::::::::::::
canine bovine mouse ovine porcine horse human rat  feline canine bovine	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ARSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNDIHSRVSQQLCSA 597  **RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSA 598  **HSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSA 598  **KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSA 598  **KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599  **********************************
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 ARSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNDIHSRVSQQLCSA 597 **RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNDIHSRVSQQLCSA 598 **HSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 **KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599 ***:********************************
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNDIHSRVSQQLCSA 597  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNDIHSRVSQQLCSA 597  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNDIHSRVSQQLCSA 598  *RSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSA 598  *KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSA 599  **********************************
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSA 597  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSA 597  *RSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSA 598  *RSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCSA 598  *KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYSA 599  ***:***:***************************
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine	*RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQQLCSA 597  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSA 598  *HSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598  *KSFSELPQLQALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598  *KSFSELPQLQALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 599  ***:*******************************
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse	*RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQQLCSA 597  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  *HSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598  *KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599  ***:*******************************
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human	*RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQQLCSA 597  *RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSA 598  *HSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598  *KSFSELPQLQALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598  *KSFSELPQLQALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 599  ***:*******************************
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPSLRYLSLAHNDIHSRVSQQLCSA 597 #RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNDIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNDIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSSRLYST 599 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSRQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQQLCST 598 #RSFTELPQLQALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQQLCST 598 #RSFTELPQLQALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQLCST 598 #RSFTELPQLSQNWAEGDLYLRFFQGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLQLL 658 #RSFTELPQLSQNWAEGDLYLRFFQGLRSLVRLDLSQNRLHTLLPRHLDNLPKSLQLL 658 #RSFTELPQLSQNWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPRHLDNLPKSLQLL 658 #RSFTELPQLSQNWAEGDLYLFFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLL 658 #RSFTELPQLSQNWAEGDLYLFFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLL 658 #RSFTELPQLSQNWAEGDLYLFFFQGLRSLIRLDLSQNRLHTLLPQTLRNLPKSLQVL 658 #RSFTELPQLSQNRAEGDLYLFFFQGLRSLIHLDLSQNRLHTLLPQTLRNLPKSLQVL 658 #RSFTELPQLSQNRAEGDLYLFFQGLRSLIHLDLSQNKLHILRPQNLNYLPKSLTKL 659 ####################################
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	#RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPRLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNDIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSSRLYST 599 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQQLCST 598 #RSFTELPQLQALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNDIHSRVSQLLCST 598 #RSFTELPQLQALDLSYNSQPFSMQGVGHNFSFVAQLPTLRYLPRSLALL 658 #RSFTELPQLSQNWAEGDLYLRFFQGLRSLVRLDLSQNRLHTLLPRTLDNLPKSLQLL 658 #RSFTELPQLSQNWAEGDLYLRFFQGLRSLVWDLSQNRLHTLLPRHLDNLPKSLQLL 658 #RSFTELPQLSQNWAEGDLYLRFFQGLRSLVWDLSQNRLHTLLPCTLGNLPKSLQLL 658 #RSFTELPQLSQNWAEGDLYLRFFQGLRSLIRLDLSQNRLHTLLPCTLGNLPKSLQLL 658 #RSFTELPQLSQNRAEGDLYLFFFQGLRSLIRLDLSQNRLHTLLPQTLRNLPKSLQVL 658 #RSFTELPQLSQNRAEGDLYLFFFQGLRSLIHLDLSQNRLHTLLPQTLRNLPKSLQVL 658 #RSFTELPQLSQNRAEGDLYLFFQGLSGLIWLDLSQNRLHTLLPQNLNYLPKSLTKL 659 #RLRDNYLAFFNWSSLVLLPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVAS 718 #RLRDNYLAFFNWSSLALLPKLEALDLAGNQLKALSNGSLPNGTQLQRLDLSGNSIGFVVP 720
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	#RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPPLEALDLSYNSQPFSMRGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQQLCSA 597 #RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598 #RSFTELPRLEALDLSYNSQPFSMQGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599  **********************************
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	#RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQQLRSA 600 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 #RSFTELPPLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQQLCSA 597 #RSFTELPPLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGIGHNFSFVAHLRTLLPRHLDNLPKSVSQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGVGHNLSFVAQLPTLRYLSAHNGIHSRVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGVGHNLSFVAQLPTLRYLSAHNGIHSRVSQQLCST 598 #RSFTELPPLEALDLSYNSQPFSMQGVGHNLSFVAQLPTLRYLSAHNGIHSRVSQQLCST 598 #RSFTELPPLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSISFVAS 718 #RLRDNYLAFFNWSSLVLLPRLEALDLAGNQLKALSNGSLPNGTQLQRLDLSSNSIGFVVP 720 #RLRDNNLAFFNWSSLTVLPRLEALDLAGNQLKALSNGSLPPGIRLQKLDVSNSIGFVVP 716 #RLRDNNLAFFNWSSLTVLPRLEALDLAGNQLKALSNGSLPPGIRLQKLDVSNSIGFVVP 716 #RLRDNNLAFFNWSSLTVLPRLEALDLAGNQLKALSNGSLPPGIRLQKLDVSNSIGFVVP 716
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline canine bovine	**RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPQLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPQLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPQLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPRLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPRLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQQLCSA 597 **RSFTELPRLEALDLSYNSQPFSMGGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSA 598 **RSFTELPRLEALDLSYNSQPFSMGGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 **KSFSELPQLQALDLSYNSQPFSMGGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599 ***********************************
canine bovine imouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	**RSFTELPRLEALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPQLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPQLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPQLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPQLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596 **RSFTELPRLEALDLSYNSQPFSMGGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCSA 597 **RSFTELPRLEALDLSYNSQPFSMGGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598 **RSFTELPRLEALDLSYNSQPFSMGGVGHNFSFVAHLRTLRHLSLAHNNIHSQVSQQLCST 598 **KSFSELPQLQALDLSYNSQPFSMQGIGHNFSFLANLSRLQNLSLAHNDIHSRVSSRLYST 599 ***:**:*:***************************
canine bovine imouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	**RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQUEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPRIEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQQLCSA 597  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPQLADLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 596  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 596  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 596  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLCSNNHAFTLLSAHNGIHSRVSQQLCST 598  ***********************************
canine bovine imouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline conine bovine mouse ovine porcine horse human rat	**RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGTHSRVSQKLSSA 596  **RRSFTELPQUEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGTHSRVSQKLSSA 596  **RSFTELPQUEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGTHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGTHSRVSQKLSSA 596  **RSFTELPRLEALDLSYNSQPFSMGGVGHNLSFVAQLPSLRYLSLAHNGTHSRVSQKLSSA 596  **RSFTELPRLEALDLSYNSQPFSMGGVGHNLSFVAQLPALRYLSLAHNDTHSRVSQQLCSA 597  **RSFTELPRLEALDLSYNSQPFSMGVGHNLSFVAQLPTLRYLSLAHNDTHSRVSQQLCST 598  **HSFTELPRLEALDLSYNSQPFSMGVGHNLSFVAQLPTLRYLSLAHNDTHSRVSQQLCST 598  **RSFTELPRLEALDLSYNSQPFSMGVGHNLSFVAQLPTLRYLSLAHNDTHSRVSQQLCST 598  **RSFTELPRLEALDLSYNSQPFSMGVGHNLSFVAQLPTLRYLSLAHNDTHSRVSQQLCST 598  **RSFTELPRLEALDLSYNSQPFSMGVGHNLSFVAQLPTLRYLSLAHNDTHSRVSQQLCST 598  **RSFTELPRLEALDLSYNSQPFSMGVGHNLSFVAQLPTLRYLSLAHNDTHSRVSQQLCST 598  **RSFTELPRLEALDLSYNSQPFSMGVGHNTSFVAHLRTLRYLSLAHNDTHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMGVGHNTSFVAHLRTLRYLSLAHNDTHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMGVGVGHNTSFVAHLRTLLSLAHNDTHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMGVGVGHNTSFVAHLRTLLSLAHNDTHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMGVGVGHNTSFVAHLRTLLSLAHNDTHSRVSQRLYST 598  **RSFTELPQLEALDLSYNSQPFSMGVGVGHNTSFVAHLRTLSLAHNDTHSRVSQKLST 598  ***********************************
canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline conine bovine mouse ovine porcine horse human rat	**RSFTELPREALDLSYNSQPFSMRGVGHNLSFVAQLPALRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQUEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPQLEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQKLSSA 596  **RSFTELPRIEALDLSYNSQPFSMQGVGHNLSFVAQLPSLRYLSLAHNGIHSRVSQQLCSA 597  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPRIEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPQLADLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 596  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 596  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 598  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLPTLRYLSLAHNGIHSRVSQQLCST 596  **RSFTELPQLEALDLSYNSQPFSMRGVGHNLSFVAQLCSNNHAFTLLSAHNGIHSRVSQQLCST 598  ***********************************

# Figure 1 (3/3)

	feline	SFFALATRLRELNLSANALKTVEPSWFGSLAGTLKVLDVTGNPLHCACGAAFVDFLLEVQ	778
	canine	SFFALAVRLRELNLSANALKTVEPSWFGSLAGALKVLDVTANPLHCACGATFVDFLLEVQ	780
	bovine	GFFVRATRLIELNLSANALKTVDPSWFGSLAGTLKILDVSANPLHCACGAAFVDFLLERQ	<i>7</i> 76
	mouse	GFFVRATRLIELNLSANALKTVDPSWFGSLAGTLKILDVSANPLHCACGAAFVDFLLERQ	-
	ovine	GFFVLANRLKELNLSANALKTVDPFWFGRLTETLNILDVSANPLHCACGAAFVDFLLEMQ	
	porcine	GFFALAKQLEELNLSANALKTVEPSWFGSMVGNLKVLDVSANPLHCACGATFVGFLLEVQ	
	horse	GFFALATRLRELNLSANALRTEEPSWFGFLAGSLEVLDVSANPLHCACGAAFVDFLLQVQ	
	human	GFFSKAKELRELNLSANALKTVDHSWFGPLASALQILDVSANPLHCACGAAFMDFLLEVQ	
	rat	AFFALAVELKEVNLSHNILKTVDRSWFGPIVMNLTVLDVSSNPLHCACGAPFVDLLLEVQ	779
		.** * .* *:*** * *:* : *** : . * :********	
	feline	AAVPGLPGHVKCGSPGQLQGRSIFAQDLRLCLDEALSWDCFGLSLLTVALGLAVPMLHHL	838
	canine	AAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDEALSWVCFSLSLLAVALSLAVPMLHQL	840
	bovine	EAVPGLSRRVTCG9PGQLQGRSIFTQDLRLCLDETLSLDCFGLSLLMVALGLAVPMLHHL	836
	mouse	EAVPGLSRRVTCGSPGQLQGRSIFTQDLRLCLDETLSLDCFGLSLLMVALGLAVPMLHHL	836
	ovine	AAVPGLSRRVTCGSPGQLQGRSIFAQDLRLCLDETLSLDCFGFSLLMVALGLAVPMLHHL	836
	porcine	AAVPGLPSRVKCGSPGQLQGHSIFAQDLRLCLDETLSWNCFGISLLAMALGLVVPMLHHL	837
	•		838
	horse	AAVPGLPSRVKCGSPGQLQGRSIFAQDLRLCLDKSLSWDCFGLSLLVVALGLAMPMLHHL	
	human	AAVPGLPSRVKCGSPGQLQGLSIFAQDLRLCLDEALSWDCFALSLLAVALGLGVPMLHHL	838
	rat	TKVPGLANGVKCGSPRQLQGRSIFAQDLRLCLDDVLSRDCFGLSLLAVAVGTVLPLLQHL	839
		****. *.*** **** ***:******* ** **.:*** :*:. :*:*::	
	feline	CGWDLWYCFHLCLAWLPRRGRRRGADALPYDAFVVFDKAQSAVADWVYNELRVRLEER	896
	canine	CGWDLWYCFHLCLAWLPRRGRRRGVDALAYDAFVVFDKAQSSVADWVYNELRVQLEER	
	bovine	CGWDLWYCFHLCLAHLPRRRRORGEDTLLYDAVVVFDKVQSAVADWVYNELRVQLEER	
	mouse	CGWDLWYCFHLCLAHLPRRRRORGEDTLLYDAVVVFDKVOSAVADWVYNELRVOLEER	
ياف القواف التي	ovine	CGWDLWYCFHLCLAHLPRRRRQRGEDTLLYDAFVVFDKAQSAVADWVYNELRVQLEER	
	porcine	CGWDLWYCFHLCLAWLPHRGQRRGADALFYDAFVVFDKAQSAVADWVYNELRVQLEER	
	horse	CGWDLWYCFHLGLAWLPRRGWQRGADALSYDAFVVFDKAQSAVADWVYNELRVRLEER	
	human	CGWDLWYCFHLCLAWLPWRGRQSGRDEDALPYDAFVVFDKTQSAVADWVYNELRGQLEEC	
		.CGWDVWYCFHLCLAWLPLLTRGR-RSAQALPYDAFVVFDKAQSAVADWVYNELRVRLEER	
		**** **** ** ** ** ** ** ***** ** ***	
who of Developing	1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1. 1	MANUFACTURE CONTRACTOR OF THE	
	feline	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL	
		RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL	958
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL	958 954
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine con contract bovine mouse	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL	958 954 954
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL	958 954 954 954
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine con constant bovine mouse ovine porcine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL	958 954 954 954 955
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine porcine horse	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRL	958 954 954 954 955 956
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	bovine mouse ovine porcine horse human	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRL RGRWALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDQVSGLLRASFLLAQQRL	958 954 954 954 955 956 958
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine porcine horse	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRWALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGCTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL	958 954 954 954 955 956 958
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	bovine mouse ovine porcine horse human	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRL RGRWALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDQVSGLLRASFLLAQQRL	958 954 954 954 955 956 958
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	bovine mouse ovine porcine horse human rat	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDQVSGLLRASFLLAQQRL RGRWALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASIYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDKVSGLLRASFLLAQQRL	958 954 954 955 956 958 958
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	bovine mouse ovine porcine horse human rat feline	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRWALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGGTLFENLWASIYGSRKTLFVLAHTDRVSGLLRTSFLLAQQRL *** *******: ***: ********************	958 954 954 955 956 958 958
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	bovine mouse ovine porcine horse human rat  feline canine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL *** *********************************	958 954 954 954 955 956 958 958 1016 1018
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine porcine horse human rat feline canine bovine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL *** *******: ***: ********************	958 954 954 954 955 956 958 958 1016 1018 1014
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine porcine horse human rat feline canine bovine mouse	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASYYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL ***********************************	958 954 954 954 955 956 958 958 1016 1018 1014
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine porcine horse human rat feline canine bovine mouse ovine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASYYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL ***********************************	958 954 954 954 955 956 958 958 1016 1018 1014 1014
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine porcine horse human rat feline canine bovine mouse ovine porcine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGCTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL *** *********************************	958 954 954 954 955 956 958 958 1016 1018 1014 1014 1014
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine porcine horse human rat feline canine bovine mouse ovine porcine horse	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGCTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL ***********************************	958 954 954 954 955 956 958 958 1016 1014 1014 1014 1015
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine porcine horse human rat feline canine bovine mouse ovine porcine horse human	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRWALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGGTLFENLWASIYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL *** *******: ***: ********************	958 954 954 954 955 956 958 958 1016 1014 1014 1014 1015 1016
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	canine bovine mouse ovine porcine horse human rat feline canine bovine mouse ovine porcine horse	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGGTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL ***********************************	958 954 954 954 955 956 958 958 1016 1014 1014 1014 1015 1016
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGGTLFENLWASIYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL *** *******: ***: ********************	958 954 954 954 955 956 958 958 1016 1014 1014 1015 1016 1018
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGGTLFENLWASIYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL *** *******: ***: ********************	958 954 954 954 955 956 958 958 1016 1018 1014 1014 1015 1018 1018
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline canine	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRWALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRWALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEEDDWLPGCTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL *** *********************************	958 954 954 954 955 956 958 958 1016 1018 1014 1014 1018 1018 1018
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGCTLFENLWASIYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEDRDWLPGQTLFENLWASIYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL *** *********************************	958 954 954 954 955 956 958 958 1016 1018 1014 1014 1015 1018 1018
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGCTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEDRDWLPGQTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL ***********************************	958 954 954 954 955 956 958 958 1016 1018 1014 1015 1016 1018 1018
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	RGRRALRCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWVPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL ***********************************	958 954 954 954 955 956 958 958 1016 1014 1014 1014 1018 1018 1018
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline conine bovine mouse ovine porcine horse human rat	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFPAQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNQ LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNR LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNR LEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNR LEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILSPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILSPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILSPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH HFYNQNFCRGPTTAE———————————————————————————————————	958 954 954 954 955 956 958 958 1016 1014 1014 1014 1018 1018 1031 1032 1032 1032 1032 1032
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat	RGRRALRICLEERDWIPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRICLEERDWIPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRICLEERDWIPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRICLEERDWIPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRICLEERDWIPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRICLEERDWIPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRICLEERDWIPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRICLEERDWIPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRICLEERDWIPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRICLEERDWIPGGTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL *** *********************************	958 954 954 954 955 956 958 958 1016 1018 1014 1014 1015 1018 1031 1032 1029 1032 1029 1031
. ১ ১৮৮ চিন্দুল ক্রিছার্টের	feline canine bovine mouse ovine porcine horse human rat  feline canine bovine mouse ovine porcine horse human rat  feline conine bovine mouse ovine porcine horse human rat	RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLARTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTMFVLDHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYGSRKTLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFENLWASVYSSRKMLFVLAHTDRVSGLLRASFLLAQQRL RGRRALRLCLEERDWLPGKTLFPAQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNQ LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGTALTRDNR LEDRKDVVVLVILRPAAYRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNR LEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNR LEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILSPDGRRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILSPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILSPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILSPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH LEDRKDVVVLVILRPDAHRSRYVRLRQRLCRQSVLLWPHQPSGQRSFWAQLGMALTRDNH HFYNQNFCRGPTTAE———————————————————————————————————	958 954 954 954 955 956 958 958 1016 1018 1014 1014 1015 1018 1031 1032 1029 1032 1032 1031 1032

Figure 2

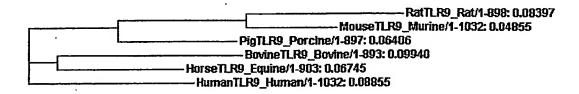
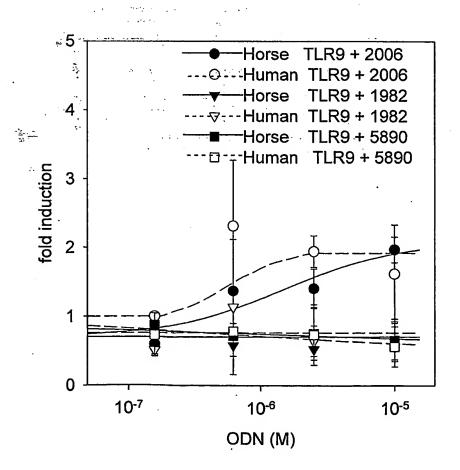


Figure 3



#### SEQUENCE LISTING

<110> Coley Pharmaceutical GmbH University of Saskatchewan Qiagen GmbH

<120> TOLL-LIKE RECEPTOR 9 (TLR9) FROM VARIOUS MAMMALIAN SPECIES

<130> C1041.70040WO00

<150> US 60/412,479

<151> 2002-09-19

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Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu

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Phe Leu Lys Ser Val Pro His Phe Ser Ala Ala Glu Pro Arg Ser Asn 50 55 60

TO STATE OF THE SAME OF THE SECOND STATE OF THE SECOND SECOND

Ile Thr Ser Leu Ser Leu Ile Ala Asn Arg Ile His His Leu His Asn 65 70 75 80

Leu Asp Phe Val His Leu Pro Asn Val Arg Gln Leu Asn Leu Lys Trp 85 90 95

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	Asn	Сув	Tyr	Tyr 180	Lys	Asn	Pro	Cys	Asn 185	Gly	Ala	Val	Asn	Val 190	Thr	Pro
	Asp	Ala	Phe 195	Leu	Gly	Leu	Ser	Asn 200	Leu	Thr	His	Leu	Ser 205	Leu	Lys	Tyr
	Asn	Asn 210	Leu	Thr	Glu	Val	Pro 215	Arg	Gln	Leu	Pro	Pro 220	Ser	Leu	Glu	Tyr
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_	Arg:	iCys:	-	*His	·Ala`	Pro	·Asp	Leu	Cys 265	Thr	Glu	Cys	Arg	Gln 270	Lys	Ser
	Leuv		Leu 275	તHis•	*Pro	Gln		∌Phe .;280	His	His	Leu	Ser	His 285	Leu	Glu	Gly
*	Leu	Val 290	Leu	· Ļys:	Asp	Sera	Ser 295	Leu	His	Ser	Leu	Asn 300	Ser	Lys	Trp	Phe
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Pro Trp Pro Ala Ser Leu Thr Pro Ala Leu Pro Ser Thr Pro Val Ser 450 450 460

Lys Asn Phe Met Val Arg Cys Lys Asn Leu Arg Phe Thr Met Asp Leu 465 470 475 480

Ser Arg Asn Asn Gln Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu 485 490 495

Ser His Leu Gln Cys Leu Ser Leu Ser His Asn Cys Ile Ala Gln Ala 500 505 510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Lys Val Leu Asp 515 520 525

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Leu Pro Glin Leu Glin Ala Leu Asp Leu Ser Tyr Asn Ser Glin Pro Phe 545 550 555

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Thr Lys Leu Ser Phe Arg Asp Asn His Leu Ser Phe Phe Asn Trp Ser 660 665 670

Ser Leu Ala Phe Leu Pro Asn Leu Arg Asp Leu Asp Leu Ala Gly Asn 675 680 685

Leu Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu 690 695 700

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Phe Val Val Pro Ala 705 710 715 720

#Phe Phe Ala Leu Ala: Val Glu Leu Lys Glu Val Asn Leu Ser His Asn 725 730 735 ing Vita to the deep

The Beu Bys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn 745 750

\*\*Eeu\*Thr\*•Val-Teu\*Asp Val Ser Ser Asn Pro Leu His Cys Ala Cys Gly
755 760 765

÷.

Ala Pro Phe Val Asp Leu Leu Glu Val Gln Thr Lys Val Pro Gly 770 780

Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Arg Gln Leu Gln Gly Arg
785 790 795 800

Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Asp Val Leu Ser 805 810 815

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Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Asp Arg Asp 900 905 910

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Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Lys Val Ser 930 935 940

Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu 945 950 955 960

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- Asn Cys Pro Pro Pro Gly Leu Ser Pro Leu His Phe Ser Cys Arg Met
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- Thr Ile Glu Pro Lys Thr Phe Leu Ala Met Arg Met Leu Glu Glu Leu 115 120 125
- Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser

2 - 4 Malle - 111 .

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- Asp Ala Phe Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205
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- Gln Gly Leu Ala Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315 320
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- Arg Lys Leu Asp Leu Ser Phe Asn Tyr Cys Lys Lys Val Ser Phe Ala 340 345 350
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- Asn Phe Ile Asn Gln Ala Gln Leu Ser Val Phe Ser Thr Phe Arg Ala 405 410 415
- Leu Arg Phe Val Asp Leu Ser Asn Asn Arg Ile Ser Gly Pro Pro Thr 420 425 430
- Leu Ser Arg Val Ala Pro Glu Lys Ala Asp Glu Ala Glu Lys Gly Val 435 440 445
- Pro Trp Pro Ala Ser Leu Thr Pro Ala Leu Pro Ser Thr Pro Val Ser 450 455 460
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- Ser Arg Asn Asn Gln Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu 485 490 495

Ser His Leu Gln Cys Leu Ser Leu Ser His Asn Cys Ile Ala Gln Ala 500 505 510

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- Leu Ser Tyr Asn Lys Leu Asp Leu Tyr His Ser Lys Ser Phe Ser Glu 530 540
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- Thr Lys Leu Ser Phe Arg Asp Asn His Leu Ser Phe Phe Asn Trp Ser 660 665 670
- Ser Leu Ala Phe Leu Pro Asn Leu Arg Asp Leu Asp Leu Ala Gly Asn 675 680 685
- Leu Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu 690 695 700
- Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Phe Val Val Pro Ala 705 710 715 720
- Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn

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ggc	2463

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- Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu Phe 35 40 45
- Leu Lys Ser Val Pro His Phe Ser Ala Ala Ala Pro Arg Ala Asn Val 50 55 60
- Thr Ser Leu Ser Leu Leu Ser Asn Arg Ile His His Leu His Asp Ser 65 70 75 80
- Asp Phe Val His Leu Ser Ser Leu Arg Thr Leu Asn Leu Lys Trp Asn 85 90 95
- Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met Thr 100 105 110
- Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn 115 120 125
- Leu Ser Tyr: Asn Ser'ile Thr Thr Vals Pro Ala Leu Pro Asp Ser Leu 130 135 140
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- His Leu Thr Gly Leu His Ala Leu Arg Tyr Leu Tyr Met Asp Gly Asn 165 170 175
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- Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn 195 200 205
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- Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asp Thr Arg Trp Phe Arg 290 295 300
- Gly Leu Asp Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr 305 310 315 320
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- Leu-His-Leu-AlamProsSer Phe Gly His Leu Arg Ser Leu Lys Glu Leu 355 360 365
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- Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly Leu 405 410 415
- Leu Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro 420 425 430
- Val Ala Ile Thr Arg Glu Val Asp Gly Arg Glu Arg Val Trp Leu Pro 435 440 445 .
- Ser Arg Asn Leu Ala Pro Arg Pro Leu Asp Thr Leu Arg Ser Glu Asp 450 455 460
- Phe Met Pro Asn Cys Lys Ala Phe Ser Phe Thr Leu Asp Leu Ser Arg 465 470 475 480

Asn Asn Leu Val Thr Ile Gln Ser Glu Met Phe Ala Arg Leu Ser Arg 485 490 495

- Leu Glu Cys Leu Arg Leu Ser His Asn Ser Ile Ser Gln Ala Val Asn 500 505 510
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- His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro 530 535 540
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- Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser Gln 580 . . . . . 585 . . . . . 590
- Gln Leu Cys Ser Ala Ser Leu Cys Ala Leu Asp Phe Ser Gly Asn Asp 595 600 600 605

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- Thr Leu Leu Pro Arg Ala Leu Asp Asn Leu Pro Lys Ser Leu Lys His
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- Leu His Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu 660 665 670
- Thr Leu Leu Pro Lys Leu Glu Thr Leu Asp Leu Ala Gly Asn Gln Leu 675 680 685
- Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Arg Arg 690 695 700
- Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Asn Pro Gly Phe Phe

705 710 715 720

Ala Leu Ala Lys Gln Leu Glu Glu Leu Asn Leu Ser Ala Asn Ala Leu 725 730 735

Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Met Val Gly Asn Leu Lys 740 745 750

Val Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Thr 755 760 765

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Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly His Ser Ile 785 790 795 800

Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Thr Leu Ser Trp Asn 805 810 815

Gys Phe Gly Ile Ser Leu Leu Ala Met Ala Leu Gly Leu Val Val Pro 820 825 830

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egGyseLeuwAla≒ErpteLeu≒Pro.His Arg Gly Gln Arg Arg Gly Ala Asp Ala 7850 --855 860

Leu-Phe Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala Val 865 870 875 880

Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Gln Leu Glu Glu Arg Arg 885 890 895

Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu Pro 900 905 910

Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser Arg 915 920 925

Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser Gly Leu Leu 930 935 940

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Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys

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Leu Lys Ser Val Pro His Phe Ser Ala Ala Pro Arg Ala Asn Val 55

Thr Ser Leu Ser Leu Ser Asn Arg Ile His His Leu His Asp Ser

Asp Phe Val His Leu Ser Ser Leu Arg Thr Leu Asn Leu Lys Trp Asn 85

Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys His Met Thr 105 100

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- His Leu Thr Gly Leu His Ala Leu Arg Tyr Leu Tyr Met Asp Gly Asn 165 170 175
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- Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn 195 200 205
- Asn Leu Thr Glu Val Pro Arg Ser Leu Pro Pro Ser Leu Glu Thr Leu 210 215 220

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- #Gys#Asp#His:Ala.\*Arg. Asn Pro Cys Arg Glu Cys Pro Lys Asp His Pro 260 265 270
- Lys Leu His Ser Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu 275 280 285
- Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asp Thr Arg Trp Phe Arg 290 295 300
- Gly Leu Asp Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr 305 310 315 320
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- Asn Asn Leu Val Thr Ile Gln Ser Glu Met Phe Ala Arg Leu Ser Arg 490 485 The second of th

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Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Arg Arg

Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Asn Pro Gly Phe Phe

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Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Met Val Gly Asn Leu Lys 740 745 750

Val Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Thr 755 760 765

Phe Val Gly Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu Pro 770 780

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Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser 70

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn Cys Pro Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys Arg Met Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn 120 Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu Val Ser Leu Ser Leu Ser His Thr Ser Ile Leu Val Leu Gly Pro Thr 150 155 His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn 165 170 175 Cys Tyr Tyr Met Asn Pro Cys Pro Arg Ala Leu Glu Val Ala Pro Gly 180 185 र ४ - १ - कार्युरस्य केंग्रे, १, श्रास्त्रकेष्ट्राच्या १, १० स्था । Ala Leu Leu Gly Leu Gly Asn Leu Thr. His Leu Ser Leu Lys Tyr Asn 200 205 4.95 ४८० । १८०० - व्यक्तिकार्यक्षात्रकार के क्षेत्रकार्यक्षात्रकार के लिए १००० व्यक्तिकार के अपने १००० व्यक्तिकार के प्राप्त के प्राप् Asn Leu Thr Glu Val Pro Arg Arg Leu Pro Pro Ser Leu Asp Thr Leu 210 rugar cares in the service in Leu Leu Ser Tyr Asn His Ile Val Thr Leu Ala Pro Glu Asp Leu Ala 235 230 Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg Arg 245 Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asn Phe Pro 260 265 , Lys Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu 275 280 Val Leu Lys Asp Ser Ser Leu Tyr Lys Leu Glu Lys Asp Trp Phe Arg 290 295 300

Gly Leu Gly Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr

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Algebra Comments of the

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535

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- Arg Ala Thr Arg Leu Ile Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys
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- Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe 755 760 765
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Arg Val Thr Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser Ile Phe 785 790 795 800

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- Phe Gly Leu Ser Leu Leu Met Val Ala Leu Gly Leu Ala Val Pro Met 820 825 830
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- Leu Tyr Asp Ala Val Val Phe Asp Lys Val Gln Ser Ala Val Ala 865 870 875 880
- Asp-Trp Val Tyr Asn Glu Leu Arg Val Gln Leu Glu Glu Arg Arg Gly 885 890 895

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بالمستعدات للبطراحة يتهاجاك

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- Val Val Leu Val Ile Leu Arg Pro Ala Ala Tyr Arg Ser Arg Tyr 965 970 975
- Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro 980 985 990
- His Gln Pro Ser Gly Gln Gly Ser Phe Trp Ala Asn Leu Gly Ile Ala 995 1000 1005
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Leu Lys Ser Val Pro His Phe Ser Ala Gly Ala Pro Arg Ala Asn Val 55 ile 1 4 4

Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser .75 80

5.3

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn 90 ... the or given a

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Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn 120

Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser Leu 135

Val Ser Leu Ser Leu Ser His Thr Ser Ile Leu Val Leu Gly Pro Thr 155

His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn 170

Cys Tyr Tyr Met Asn Pro Cys Pro Arg Ala Leu Glu Val Ala Pro Gly 185

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- ... Gly:Leu:Gly:ArgeLeu-Gln:Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr : 330 315 320
- ##Asp%Tyrille #Thrallys #Thrathr Ile Phe Asn Asp Leu Thr Gln Leu Arg

The Control of

19.5

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- Leu His Leu Ala Ser Ser Phe Gly Ser Leu Val Ser Leu Glu Lys Leu 355 360 365
- Asp Met His Gly Ile Phe Phe Arg Ser Leu Thr Asn Ile Thr Leu Gln 370 380
- Ser Leu Thr Arg Leu Pro Lys Leu Gln Ser Leu His Leu Gln Leu Asn 385 390 395 400
- Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu 405 410 415
- Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Thr Pro

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Gln Cys Leu Arg Leu Ser His Asn Ser Fle Ser Gln Ala Val Asn Gly 500 505 510

Ser Gln Phe Val Pro Leu Thr Ser Leu Arg Val Leu Asp Leu Ser His 515 520 525

Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Gln 530 540

Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln 545 550 555 560

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Leu Arg Asn Leu Val Gln Leu Asp Leu Ser Glu Asn His Leu His Thr 625 630 635 640

Leu Leu Pro Arg His Leu Asp Asn Leu Pro Lys Ser Leu Arg Gln Leu 645 650 655

Arg Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu Thr 660 665 Val Leu Pro Arg Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Pro Gly Ile Arg Leu Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Gly Phe Val Ile Pro Gly Phe Phe Val 705 Arg Ala Thr Arg Leu Ile Glu Leu Asn Leu Ser Ala Asn Ala Leu Lys 725 Thr Val Asp Pro Ser Trp Phe Gly Ser Leu Ala Gly Thr Leu Lys Ile 740 Leu Asp Val Ser Ala Asn Pro Leu His Cys Ala Cys Gly Ala Ala Phe 765 ⇒Val∰Asp Phe BeumLeu Glu Argi Gln Glu Ala Val Pro Gly Leu Ser Arg **~7.70** ~.775 - Arg WalkThr Gys Gly Ser Pro Gly Gladeu Gla Gly Arg Ser Ile Phe n≠785 790 795 Thr Gln Asp Leu Arg Leu Cys Leu Asp Glu Thr Leu Ser Leu Asp Cys æ≈80**5** 810 Phe Gly <210> 11 <211> 3191 <212> DNA <213> Bos taurus <400> 11 gggaagtggg cgccaagcat cettecetge agetgcetec caacetgcec gccagacect 60 ctggagaagc cgcattccct gtcatgggcc cctactgtgc cccgcacccc ctttctctcc 120 tggtgcaggc ggcggcactg gcagcggccc tggccgaggg caccctqcct gccttcctqc 180 cetgtgaget ccagececat ggteaggtgg actgeaactg getgtteetg aagtetgtge 240 cgcacttttc ggctggagcc ccccgggcca atgtcaccag cctctcctta atctccaacc 300

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भ अध्यक्षितसम्बद्धाः । अ

ন্ধনীয় ক্রিক্রাক্রিক এই মুক্ত ক্রেক্ট্রাম ক্রিক্ট্রেক এই এই

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Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 135 140

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- His Leu Thr Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu 355 360 365
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Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser 915 920 925

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Asn Cys Tyr Tyr Lys Asn Pro Cys Gly Arg Ala Leu Glu Val Ala Pro 180 185 190

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- His Leu Thr Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu 355 360 365
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Asn Gly Ser Gln Phe Val Pro Leu Thr Ser Leu Gln Val Leu Asp Leu
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- Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu 530 535 540
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- Ser Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg Phe Phe 610 620
- Gln Gly Leu Arg-Ser Leu Ile Arg Leu Asp Leu Ser Gln Asn Arg Leu 625 630 635 640
- His Thr Leu Leu Pro Cys Thr Leu Gly Asn Leu Pro Lys Ser Leu Gln
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- Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Ser Gly Thr Gln Leu Gln 690 695 700
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eriki ya Tangan da karasa

 $e^{i t} \left( 4 \sigma_{i}^{2} \left( \phi_{i, t}^{2} \right) \right) \left( 4 \frac{d t}{2} \right) = 0 \quad \forall i \in \mathbb{N}$ 

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Leu Lys Ser Val Pro Arg Phe Ser Ala Gly Ala Pro Arg Ala Asn Val 50 55 60

Thr Ser Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asp Ser 65 70 75 80

Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn 85 90 95

TGys Pro Ala Gly Leu Ser Pro Met His Phe Pro Cys Arg Met Thr

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The Glu-ProvAsn Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu Asn 编扫5 120 125

Leu SeraTyreAsneGly: The Thr Val Pro Ala Leu Pro Ser Ser Leu 130 135 140

Val Ser Leu Ser Leu Ser Arg Thr Ser Ile Leu Val Leu Gly Pro Thr 145 150 155 160

His Phe Thr Gly Leu His Ala Leu Arg Phe Leu Tyr Met Asp Gly Asn 165 170 175

Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Val Glu Val Ala Pro Gly 180 185 190

Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr Asn 195 200 205

Asn Leu Thr Glu Val Pro Arg Arg Leu Pro Pro Ser Leu Asp Thr Leu 210 215 220

Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Asn Cys Arg Arg Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Asn Phe Pro 265 Lys Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly Leu 280 Val Leu Lys Asp Ser Ser Leu Tyr Lys Leu Glu Lys Asp Trp Phe Arg Gly Leu Gly Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr 315 305 310 Asp Tyr Ile Thr Lys Thr Thr Ile Phe Arg Asn Leu Thr Gln Leu Arg 330 325 335 Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His 7340 345 350 e de la composiçõe de la composição de la composiç Leu Gln Leu Ala Pro Ser Phe Gly Gly Leu Val Ser Leu Glu Lys Leu 355 - in 360° weeksaultogen a til tro 365 i seen med to . The second secon Asp Met His Gly Ile Phe Phe Arg Ser Leu Thr Asn Thr Thr Leu Arg 370 375 Pro Leu Thr Gln Leu Pro Lys Leu Gln Ser Leu Ser Leu Gln Leu Asn 385 390 395 Phe Ile Asn Gln Ala Glu Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu 405 415 Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro 420 425 430 Val Ala Ala Leu Gly Glu Val Asp Ser Gly Val Glu Val Trp Arg Trp 435 440 445

Pro Arg Gly Leu Ala Pro Gly Pro Leu Ala Ala Val Ser Ala Lys Asp

455

450

Phe Met Pro Ser Cys Asn Leu Asn Phe Thr Leu Asp Leu Ser Arg Asn 465 . 470 475 480

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- Ser Gln Phe Val Pro Leu Thr Arg Leu Arg Val Leu Asp Leu Ser Tyr 515 520 525
- Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu Pro Gln 530 535 540
- Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser Met Gln 545 550 555 560
- Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ser Leu Arg

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4 . 1964 4 982 . 38

A. A. 3

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- Ser-Gln\*Met Trp:Ala Glu Gly Asp Leu Tyr Leu Cys Phe Phe Lys Gly 610" 620
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  - Leu Leu Pro Arg His Leu Asp Asn Leu Pro Lys Ser Leu Arg Gln Leu 645 650 655
  - Arg Leu Arg Asp Asn Asn Leu Ala Phe Phe Asn Trp Ser Ser Leu Thr 660 665 670
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Asp Val Ser Ser Asn Ser Ile Gly Phe Val Thr Pro Gly Phe Phe Val 705 710 715 720

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- Leu Ala His Leu Pro Arg Arg Arg Gln Arg Gly Glu Asp Thr Leu 850 855 860
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- Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser Arg Lys 915 920 925
- Thr Met Phe Val Leu Asp His Thr Asp Arg Val Ser Gly Leu Leu Arg

930 935 940

Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg Lys Asp 945 950 955 960

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Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu Trp Pro 980 985 990

His Gln Pro Ser Gly Gln Gly Ser Phe Trp Ala Asn Leu Gly Met Ala 995 1000 1005

Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Arg Asn Phe Cys Arg 1010 1015 1020

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Section 1

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Asp Phe Val His Leu Ser Asn Leu Arg Val Leu Asn Leu Lys Trp Asn 85 90 95

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Gly Leu Gly Arg Leu Gln Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr

Asp Tyr Ile Thr Lys Thr Thr Ile Phe Arg Asn Leu Thr Gln Leu Arg

305

1.2

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- Phe Ile Asn Gln Ala Glu Leu Ser Ile Phe Gly Ala Phe Pro Ser Leu 405 410 415
- Leu Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Arg Pro 420 425 430
- Val-Ala Ala Leu Gly Glu Val Asp Ser Gly Val Glu Val Trp Arg Trp

St. L. British

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المارية المراجع المراجع

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Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg Val Ser Gln Lys
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#aacccctgcc.agcaggccgt.ggaggtggcc.ccaggcgccc tccttggcct gggcaacctc	600	a selfaceal not have seen a
*acgcacctgtacgctcaagta caacaacctcaacggaggtgc cccgccgcct gcccccagc	660	్ కార్యాట్ ఈ స్ట్రిక్స్తోన్నారు.
**ceggaeaccc***egcegetegete ctacaaccac atcatcaccc tggcacccga ggacctggcc	720	engle between the American of g
جيءatctgactg	780	अस्टिम्स्य स्टाउक्का स्टब्स
wicgcaacccct*gcagggagtg cccaaagaac ttccccaagc tgcaccctga caccttcagc	840	் வநைகளை உள்ள
caccegagecracecegaagg cetggtgttg aaggacagtt etetetacaa aetagagaaa	900	को साम्बन्धिकी संस्थान सुर्वे । १०००
gactggttcc.gcggcctggg caggctccaa gtgctcgacc tgagtgagaa cttcctctat	960	· · · · · · · · · · · · · · · · · · ·
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State Alexander of Section 19

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ويتوني فيحرين

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<211> 1032 <212> PRT

<213> Canis familiaris

<400> 21

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Ala Ala Ala Leu Ala Leu Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe 20 25 30

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu 35 40 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Pro Arg Gly Asn 50 60

Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp 65 70 75 80

Tyr Asp Phe Val His Phe Val His Leu Arg Arg Leu Asn Leu Lys Trp 85 90 95

- Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met 100 105 110
- Thr Ile Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Asp Leu 115 120 125
- Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 140
- Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro 145 150 155 160
- Ala Thr Leu Ala Gly Leu Tyr Ala Leu Arg Phe Leu Phe Leu Asp Gly
  165 170 175
- Asn Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Leu Gln Val Ala Pro 180 185 190
- ∴Gly:AlatLeu:Leu:Gly:Leu:Gly:Asn Leu Thr His Leu Ser Leu Lys Tyr
  10195 200 205

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(28)

- AsnyAsnyLeusThreVal=ValyPro∴Arg Gly Leu Pro Pro Ser Leu Glu Tyr 3210 220
- ELEU-Leu-Leu-Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu 225 230 235 240
- Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg 245 250 255
- Arg Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Gly Phe 260 265 270
- Pro Gln Leu His Pro Asn Thr Phe Gly His Leu Ser His Leu Glu Gly 275 280 285
- Leu Val Leu Arg Asp Ser Ser Leu Tyr Ser Leu Asp Pro Arg Trp Phe 290 295 300
- His Gly Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315

Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala 350

His Leu His Leu Ala Ser Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu 355

Leu Asp Ile His Gly Ile Phe Phe Arg Ser Leu Ser Lys Thr Thr Leu 370

Gln Ser Leu Ala His Leu Pro Met Leu Gln Arg Leu His Leu Gln Leu 385

Asn Phe Ile Ser Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly 410

Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Glu 425

Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Tyr Gly Leu Ala Arg Leu

Pro Ala Ala Ala Thr Gly Glu Val Glu Ala Asp Cys Gly Glu Arg Val
435

Trp Pro Gln Ser Arg Asp Leu Ala Leu Gly Pro Leu Gly Thr Pro Gly 450 455 460.

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Ser Glu Ala Phe Met Pro Ser Cys Arg Thr Leu Asn Phe Thr Leu Asp 465 470 475 480

Leu Ser Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Val Arg 485 490 495

Leu Ala Arg Leu Gln Cys Leu Gly Leu Ser His Asn Ser Ile Ser Gln 500 505 510

Ala Val Asn Gly Ser Gln Phe Val Pro Leu Ser Asn Leu Arg Val Leu 515 520 525

Asp Leu Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr 530 540

Glu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro

Phe Ser Met Arg Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu 575

Pro Ala Leu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg 580

Val Ser Gln Gln Leu Arg Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser 600

Gly Asn Thr Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg 610

Phe Phe Gln Gly Leu Arg Ser Leu Val Gln Leu Asp Leu Ser Gln Asn 625 630 635 640

Arg Leu His Thr Leu Leu Pro Arg Asn Leu Asp Asn Leu Pro Lys Ser 645 650 655

\*\*Leu#Arg\*Eeu\*Arg Leu\*Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp
\*\*660 -665 670

Liver and Jean reading

Ser Ser Leu Ala Heu Leu Pro Lys Leu Glu Ala Leu Asp Leu Ala Gly 4675 680 685

Asnt Gln Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln 690 695 700

Leu Gln Arg Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Val Pro 705 710 715 720

Ser Phe Phe Ala Leu Ala Val Arg Leu Arg Glu Leu Asn Leu Ser Ala 725 730 735

Asn Ala Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly 740 745 750

Ala Leu Lys Val Leu Asp Val Thr Ala Asn Pro Leu His Cys Ala Cys 755 760 765

Gly Ala Thr Phe Val Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro 770 775 780 Gly Leu Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly 785 790 795 800

- Arg Ser Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu 805 810 815
- Ser Trp Val Cys Phe Ser Leu Ser Leu Leu Ala Val Ala Leu Ser Leu 820 825 830
- Ala Val Pro Met Leu His Gln Leu Cys Gly Trp Asp Leu Trp Tyr Cys 835 840 845
- Phe His Leu Cys Leu Ala Trp Leu Pro Arg Arg Gly Arg Arg Arg Gly 850 860
- Val Asp Ala Leu Ala Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln 865 870 875 888
- Ser Ser Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Gln Leu Glu 885 890 895
- Glu Arg Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp 900 905 910 910
- Trp Val Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr 915 920 925 925
- Ser Ser Arg Lys Thr Leu Phe Val Leu Ala Arg Thr Asp Arg Val Ser 930 935 940
- Gly Leu Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu 945 950 955 960
- Asp Arg Lys Asp Val Val Val Leu Val Ile Leu Cys Pro Asp Ala His
  965 970 975
- Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val 980 985 990
- Leu Leu Trp Pro His Gla Pro Ser Gly Gln Arg Ser Phe Trp Ala Gla 995 1000 1005
- Leu Gly Thr Ala Leu Thr Arg Asp Asn Arg His Phe Tyr Asn Gln 1010 1015 1020

Asn Phe Cys Arg Gly Pro Thr Thr Ala 1025 1030

<210> 22

<211> 822

<212> PRT

<213> Canis familiaris

<400> 22

Met Gly Pro Cys Arg Gly Ala Leu His Pro Leu Ser Leu Leu Val Gln 1 5 10 15

Ala Ala Ala Leu Ala Leu Ala Gln Gly Thr Leu Pro Ala Phe 20 25 30

Leu Pro Cys Glu Leu Gln Pro His Gly Leu Val Asn Cys Asn Trp Leu 35 40 . 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Pro Arg Gly Asn \$\frac{1}{2750}\$ 55 60

Wall Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp

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Takan Property Sanct

\*\*Thr: Fle Glu Pro Asn Thr Phe Leu Ala Val Pro Thr Leu Glu Asp Leu
115 120 125

Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 135 140

Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro

Ala Thr Leu Ala Gly Leu Tyr Ala Leu Arg Phe Leu Phe Leu Asp Gly
165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Gln Gln Ala Leu Gln Val Ala Pro 180 185 190 Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr 200

- Asn Asn Leu Thr Val Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr
- Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu
- Ala Asn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Asn Cys Arg 250
- Arg Cys Asp His Ala Arg Asn Pro Cys Arg Glu Cys Pro Lys Gly Phe , 265
- Pro Gln Leu His Pro Asn Thr Phe Gly His Leu Ser His Leu Glu Gly 280
- Leu Val Leu Arg Asp Ser Ser Leu Tyr Ser Leu Asp Pro Arg Trp Phe 295 and the second of the second o
- His Gly Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu 315 The second secon

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- Tyr Asp Cys Ile Thr Lys Thr Lys Ala Phe Tyr Gly Leu Ala Arg Leu 325 330 The second of the second second
- Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala 340 345
- His Leu His Leu Ala Ser Ser Phe Gly Ser Leu Leu Ser Leu Gln Glu
- Leu Asp Ile His Gly Ile Phe Phe Arg Ser Leu Ser Lys Thr Thr Leu
- Gln Ser Leu Ala His Leu Pro Met Leu Gln Arg Leu His Leu Gln Leu 390 395 385
- Asn Phe Ile Ser Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly 405 410
- Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Ala Glu 420 425

Pro Ala Ala Thr Gly Glu Val Glu Ala Asp Cys Gly Glu Arg Val
435 . 440 445

Trp Pro Gln Ser Arg Asp Leu Ala Leu Gly Pro Leu Gly Thr Pro Gly 450 455 460

Ser Glu Ala Phe Met Pro Ser Cys Arg Thr Leu Asn Phe Thr Leu Asp 465 470 475 480

Leu Ser Arg Asn Asn Leu Val Thr Val Gln Pro Glu Met Phe Val Arg 485 490 495

Leu Ala Arg Leu Gln Cys Leu Gly Leu Ser His Asn Ser Ile Ser Gln 500 505 510

Ala Val Asn Gly Ser Gln Phe Val Pro Leu Ser Asn Leu Arg Val Leu 515 520 525

-Asp LeurSer-His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr -53.0 2535 540 The same of the same

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#GluwLeuwProwArgwLeuwGluwAla Leu Asp Leu Ser Tyr Asn Ser Gln Pro ##545 \$550 555 560

##PherserwMetrargeGly/ValuGly His Asn Leu Ser Phe Val Ala Gln Leu 575 575

Pro AlamLeu Arg Tyr Leu Ser Leu Ala His Asn Gly Ile His Ser Arg 580 585 590

Val Ser Gln Gln Leu Arg Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser 595 600 605

Gly Asn Thr Leu Ser Gln Met Trp Ala Glu Gly Asp Leu Tyr Leu Arg 610 615 620

Phe Phe Gln Gly Leu Arg Ser Leu Val Gln Leu Asp Leu Ser Gln Asn 625 630 635 640

Arg Leu His Thr Leu Leu Pro Arg Asn Leu Asp Asn Leu Pro Lys Ser 645 650 655

Leu Arg Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp

Ser Ser Leu Ala Leu Leu Pro Lys Leu Glu Ala Leu Asp Leu Ala Gly 675 680 685

Asn Gln Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln 690 695 700

Leu Gln Arg Leu Asp Leu Ser Gly Asn Ser Ile Gly Phe Val Val Pro
705 710 715 720

Ser Phe Phe Ala Leu Ala Val Arg Leu Arg Glu Leu Asn Leu Ser Ala 725 730 735

Asn Ala Leu Lys Thr Val Glu Pro Ser Trp Phe Gly Ser Leu Ala Gly 740 745 750

Ala Leu Lys Val Leu Asp Val Thr Ala Asn Pro Leu His Cys Ala Cys 755 760 765

Gly Leu Pro Ser Arg Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly 785 790 795 795 795 800

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2.

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Phe Leu Lys-Ser Val Pro His Phe Ser Ala Ala Pro Arg Gly Asn . 50 55

3.5

Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp 65 75

Ser Asp Phe Val His Leu Ser Ser Leu Arg Arg Leu Asn Leu Lys Trp 95 90

Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met 100 110

Thr Ile Glu Pro His Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu 115

Asn Leu Ser Tyr Asn Ser Ile Thr Thr Val Pro Ala Leu Pro Ser Ser 130 135

Leu Val Ser Leu Ser Leu Ser Arg Thr Asn Ile Leu Val Leu Asp Pro 145 Ala Asn Leu Ala Gly Leu His Ser Leu Arg Phe Leu Phe Leu Asp Gly 165 Asn Cys Tyr Tyr Lys Asn Pro Cys Pro Gln Ala Leu Gln Val Ala Pro 180 Gly Ala Leu Leu Gly Leu Gly Asn Leu Thr His Leu Ser Leu Lys Tyr 200 Asn Asn Leu Thr Ala Val Pro Arg Gly Leu Pro Pro Ser Leu Glu Tyr 215 Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu 230 235 AlawAsn Leu Thr Ala Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg 250 Argaeys: Aspathis. Ala: Arg Asn Pro Cys Met Glu Cys Pro Lys Gly Phe ±e2.60 265 Pro His Leu His Pro Aspathr Phe Ser His Leu Asn His Leu Glu Gly 280 2:75 تنسم Leu Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asn Pro Arg Trp Phe 295 His Ala Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu 315 Tyr Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Gln Leu 325 Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala His Leu His Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Gln 360

Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Glu Thr Thr Leu

375

Arg Ser Leu Val His Leu Pro Met Leu Gln Ser Leu His Leu Gln Met 385 390 395 400

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- Leu Ala Ala Thr Gly Glu Val Asp Gly Gly Glu Arg Val Arg Leu
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- Pro Ser Gly Asp Leu Ala Leu Gly Pro Pro Gly Thr Pro Ser Ser Glu 450 455 460
- Gly Phe Met Pro Gly Cys Lys Thr Leu Asn Phe Thr Leu Asp Leu Ser 465 470 480
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- Asn GlyrSer Gln Phe Met Pro Leu Thr Ser Leu Gln Val Leu Asp Leu S515 520 Ser Leu Gln Val Leu Asp Leu S525 ...

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- Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu 530 535 540
- Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser 545 550 555
- Met Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala 565 570 575
- Leu Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser 580 585 590
- Gln Gln Leu Cys Ser Ala Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn 595 600 605
- Ala Leu Ser Arg Met Trp Ala Glu Gly Asp Leu Tyr Leu His Phe Phe

610 615 620

Arg Gly Leu Arg Ser Leu Val Arg Leu Asp Leu Ser Gln Asn Arg Leu 625 630 635

His Thr Leu Leu Pro Arg Thr Leu Asp Asn Leu Pro Lys Ser Leu Arg 645 650 655

Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp Ser Ser 660 665 670

Leu Val Leu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln 675 680 685

Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln Leu Gln 690 695 700

Arg Leu Asp Leu Ser Ser Asn Ser Ile Ser Phe Val Ala Ser Ser Phe 705 710 715 720

Phe Ala-Leu Ala Thr Arg Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala 725 730 735

Leuk-LysigthraVal和Glu+PropSer/Trp Phe Gly Ser Leu Ala Gly Thr Leu 740 745 750

man delta Total

\*\*Lys\*Val\*Leu\*Asp Val\*Thr\* Gly Asn Pro Leu His Cys Ala Cys Gly Ala \*\*755 760 765

Ala PherVal Asp Phe Leu Leu Glu Val Gln Ala Ala Val Pro Gly Leu 770 775 780

Pro Gly His Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser 785 790 795 800

Ile Phe Ala Gln Asp Leu Arg Leu Cys Leu Asp Glu Ala Leu Ser Trp 805 810 815

Asp Cys Phe Gly Leu Ser Leu Leu Thr Val Ala Leu Gly Leu Ala Val 820 825 830

Pro Met Leu His His Leu Cys Gly Trp Asp Leu Trp Tyr Cys Phe His 835 840 845 Leu Cys Leu Ala Trp Leu Pro Arg Arg Gly Arg Arg Gly Ala Asp 850 855 860

Ala Leu Pro Tyr Asp Ala Phe Val Val Phe Asp Lys Ala Gln Ser Ala 865 870 875 880

Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu Glu Arg 885 890 895

Arg Gly Arg Arg Ala Leu Arg Leu Cys Leu Glu Glu Arg Asp Trp Leu 900 905 910

Pro Gly Lys Thr Leu Phe Glu Asn Leu Trp Ala Ser Val Tyr Ser Ser 915 920 925

Arg Lys Met Leu Phe Val Leu Ala His Thr Asp Arg Val Ser Gly Leu 930 935 940

Leu Arg Ala Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu Asp Arg 945 950 955 960

Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val Leu Leu 980 985. 990

Trp Pro His Gln Pro Ser Gly Gln Arg Ser Phe Trp Ala Gln Leu Gly 995 1000 1005

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Cys Arg Gly Pro Thr Thr Ala Glu 1025 1030

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- Val Thr Ser Leu Ser Leu Tyr Ser Asn Arg Ile His His Leu His Asp 65 70 75 80
- Ser Asp Phe Val His Leu Ser Ser Leu Arg Arg Leu Asn Leu Lys Trp 85 90 95
- Asn Cys Pro Pro Ala Ser Leu Ser Pro Met His Phe Pro Cys His Met 100 105 110
- Thr Ile Glu Pro His Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu 115 120 125

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and the second

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  175
- AşnıçCys TyrrTyr Lys AsnıPro Cys Pro Gln Ala Leu Gln Val Ala Pro 180 185 190
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- Leu Leu Ser Tyr Asn His Ile Ile Thr Leu Ala Pro Glu Asp Leu 225 230 235 240
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Arg Cys Asp His Ala Arg Asn Pro Cys Met Glu Cys Pro Lys Gly Phe 265 Pro His Leu His Pro Asp Thr Phe Ser His Leu Asn His Leu Glu Gly 280 Leu Val Leu Lys Asp Ser Ser Leu Tyr Asn Leu Asn Pro Arg Trp Phe 295 His Ala Leu Gly Asn Leu Met Val Leu Asp Leu Ser Glu Asn Phe Leu Tyr Asp Cys Ile Thr Lys Thr Thr Ala Phe Gln Gly Leu Ala Gln Leu Arg Arg Leu Asn Leu Ser Phe Asn Tyr His Lys Lys Val Ser Phe Ala 345 His Leu His Leu Ala Pro Ser Phe Gly Ser Leu Leu Ser Leu Gln Gln 360 Leu Asp Met His Gly Ile Phe Phe Arg Ser Leu Ser Glu Thr Thr Leu The state of the second state of the second \*\*... Arg Ser Leu Val His Leu Pro Met Leu Gln Ser Leu His Leu Gln Met 395 390 385 Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Ala Phe Pro Gly 410 Leu Arg Tyr Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Ala Met Glu 425 Leu Ala Ala Ala Thr Gly Glu Val Asp Gly Glu Arg Val Arg Leu 435 Pro Ser Gly Asp Leu Ala Leu Gly Pro Pro Gly Thr Pro Ser Ser Glu Gly Phe Met Pro Gly Cys Lys Thr Leu Asn Phe Thr Leu Asp Leu Ser 475 465

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Arg Asn Asn Leu Val Thr Ile Gln Pro Glu Met Phe Ala Arg Leu Ser

Arg Leu Gln Cys Leu Leu Ser Arg Asn Ser Ile Ser Gln Ala Val 500 505 510

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  515 520 525
- Ser His Asn Lys Leu Asp Leu Tyr His Gly Arg Ser Phe Thr Glu Leu 530 540
- Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Ser 545 550 555 560
- Met Gln Gly Val Gly His Asn Leu Ser Phe Val Ala Gln Leu Pro Ala 565 570 575
- Leu Arg Tyr Leu Ser Leu Ala His Asn Asp Ile His Ser Arg Val Ser 580 585 590
- Gln Gln-Leu: Cys#Ser Ala\*Ser Leu Arg Ala Leu Asp Phe Ser Gly Asn ~595 600 605

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1.00

- Arg Gly Leu Arg Ser Leu Asp Leu Ser Gln Asn Arg Leu 625 630 635 640
  - HistThr Leu Leu Pro Arg Thr Leu Asp Asn Leu Pro Lys Ser Leu Arg 645 650 655
  - Leu Leu Arg Leu Arg Asp Asn Tyr Leu Ala Phe Phe Asn Trp Ser Ser 660 665 670
  - Leu Val Leu Leu Pro Arg Leu Glu Ala Leu Asp Leu Ala Gly Asn Gln 675 680 685
  - Leu Lys Ala Leu Ser Asn Gly Ser Leu Pro Asn Gly Thr Gln Leu Gln 690 695 700
  - Arg Leu Asp Leu Ser Ser Asn Ser Ile Ser Phe Val Ala Ser Ser Phe 705 710 715 720
  - Phe Ala Leu Ala Thr Arg Leu Arg Glu Leu Asn Leu Ser Ala Asn Ala

725 730 735

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Lys Val Leu Asp Val Thr Gly Asn Pro Leu His Cys Ala Cys Gly Ala 755 760 765

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Pro Gly His Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg Ser 785 790 795 800

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Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu 35 40 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ser Cys Ser Asn 50 55 60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn 65 70 75 80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp 85 90 95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met 100 105 110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu 115

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- 4

Asn Leu Ser Tyr Asn Gly Ile Thr Thre Vale Pro Arg Leu Pro Ser Ser 130 140

Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala 145 150 155 160

Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly 165 170 175

Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro 180 185 190

Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205

Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr 210 215 220

Leu Leu Val Ser Tyr Asn Leu Ile Val Lys Leu Gly Pro Glu Asp Leu

235 225 230 240 Ala Asn Leu Thr Ser Leu Arg Val Leu Asp Val Gly Gly Asn Cys Arg 245 250 Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser 265 Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly 280 Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe 295 Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu 315 310 Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu 325 330 Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala 340 345 \*\*\*Argebeu#HissLeuVAla#Ser#Ser\*Phe Lys Asn Leu Val Ser Leu Gln Glu <del>~~3</del>55 360 \*Leu-AsneMet-AsneGly TletPhe Phe Arg Ser Leu Asn Lys Tyr Thr Leu 380 £370 ÷375 Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met 390 395 Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala 410 Leu Arg Phe Val Asp Leu Ser Asp Asn Arg Ile Ser Gly Pro Ser Thr 425 Leu Ser Glu Ala Thr Pro Glu Glu Ala Asp Asp Ala Glu Glu Glu 440

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Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser

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Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu 465 470 Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu 490 Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala 505 Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp 520 Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu 535 Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe 560 555 Ser Met Lys Gly Ile Gly His Asn Phe Ser Phe Val Ala His Leu Ser 570 575 565 Met Leu His Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val 585 580 Ser Ser His Leu Asn Ser Asn Ser Val Arg Phe Leu Asp Phe Ser Gly 595 - 600 <u>Grand Representation 605</u> Asn Gly Met Gly Arg Met Trp Asp Glu Gly Gly Leu Tyr Leu His Phe 615 620 610 Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn 635 625 630 Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu

650 655 645

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- Lys Leu Leu Ser Leu Arg Asp Asn Tyr Leu Ser Phe Phe Asn Trp Thr 665 660
- Ser Leu Ser Phe Leu Pro Asn Leu Glu Val Leu Asp Leu Ala Gly Asn 675 680
- Gln Leu Lys Ala Leu Thr Asn Gly Thr Leu Pro Asn Gly Thr Leu Leu 695 690

Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala 705 710 715 720

- Phe Phe Ala Leu Ala Val Glu Leu Lys Glu Val Asn Leu Ser His Asn 725 730 735
- Ile Leu Lys Thr Val Asp Arg Ser Trp Phe Gly Pro Ile Val Met Asn 740 745 750
- Leu Thr Val Leu Asp Val Arg Ser Asn Pro Leu His Cys Ala Cys Gly
  755 760 765
- Ala Ala Phe Val Asp Leu Leu Glu Val Gln Thr Lys Val Pro Gly 770 780
- Leu Ala Asn Gly Val Lys Cys Gly Ser Pro Gly Gln Leu Gln Gly Arg 785 790 795 800
- Serfile PhelAla-GlntAsp Leu Arg Leu Cys Leu Asp Glu Val Leu Ser 1805 810 815
- Trp.Asp.Gys.Phe:Gly.Leu-Ser Leu Leu Ala Val Ala Val Gly Met Val \*820 825 830
- ValvePro€He-Leu®HistHist-Leu Cys Gly Trp Asp Val Trp Tyr Cys Phe

  \*\*835

  845
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  - Ser Ala Val Ala Asp Trp Val Tyr Asn Glu Leu Arg Val Arg Leu Glu 885 890 895
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  - Trp Leu Pro Gly Gln Thr Leu Phe Glu Asn Leu Trp Ala Ser Ile Tyr 915 920 925
  - Gly Ser Arg Lys Thr Leu Phe Val Leu Ala His Thr Asp Arg Val Ser 930 935 940

Gly Leu Leu Arg Thr Ser Phe Leu Leu Ala Gln Gln Arg Leu Leu Glu 945 950 955 960

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965 970 975

Arg Ser Arg Tyr Val Arg Leu Arg Gln Arg Leu Cys Arg Gln Ser Val 980 985 990

Leu Phe Trp Pro Gln Gln Pro Asn Gly Gln Gly Gly Phe Trp Ala Gln 995 1000 1005

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Asn Phe Cys Arg Gly Pro Thr Ala Glu 1025 1030

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Leu Pro Cys Glu Leu Lys Pro His Gly Leu Val Asp Cys Asn Trp Leu 35 40 45

Phe Leu Lys Ser Val Pro Arg Phe Ser Ala Ala Ala Ser Cys Ser Asn 50 55 60

Ile Thr Arg Leu Ser Leu Ile Ser Asn Arg Ile His His Leu His Asn 65 70 75 80

Ser Asp Phe Val His Leu Ser Asn Leu Arg Gln Leu Asn Leu Lys Trp
85 90 95

Asn Cys Pro Pro Thr Gly Leu Ser Pro Leu His Phe Ser Cys His Met 100 105 110

Thr Ile Glu Pro Arg Thr Phe Leu Ala Met Arg Thr Leu Glu Glu Leu 115 120 125

- Asn Leu Ser Tyr Asn Gly Ile Thr Thr Val Pro Arg Leu Pro Ser Ser 130 135 140
- Leu Val Asn Leu Ser Leu Ser His Thr Asn Ile Leu Val Leu Asp Ala 145 150 155 160
- Asn Ser Leu Ala Gly Leu Tyr Ser Leu Arg Val Leu Phe Met Asp Gly 165 170 175
- Asn Cys Tyr Tyr Lys Asn Pro Cys Thr Gly Ala Val Lys Val Thr Pro 180 185 190
- Gly Ala Leu Leu Gly Leu Ser Asn Leu Thr His Leu Ser Leu Lys Tyr 195 200 205
- Asn Asn Leu Thr Lys Val Pro Arg Gln Leu Pro Pro Ser Leu Glu Tyr 210 220

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©Leu©Leu®ValeSer®TyreAsneLeu Ile Val Lys Leu Gly Pro Glu Asp Leu ©225 230 235 240

Sec. 1

- AlawAsneLeu ThreSer LeuwArg: Val Leu Asp Val Gly Gly Asn Cys Arg 25245 250 255
- Arg Cys Asp His Ala Pro Asn Pro Cys Ile Glu Cys Gly Gln Lys Ser
  - Leu His Leu His Pro Glu Thr Phe His His Leu Ser His Leu Glu Gly 275 280 285
  - Leu Val Leu Lys Asp Ser Ser Leu His Thr Leu Asn Ser Ser Trp Phe 290 295 300
  - Gln Gly Leu Val Asn Leu Ser Val Leu Asp Leu Ser Glu Asn Phe Leu 305 310 315 320
  - Tyr Glu Ser Ile Asn His Thr Asn Ala Phe Gln Asn Leu Thr Arg Leu 325 330 335
  - Arg Lys Leu Asn Leu Ser Phe Asn Tyr Arg Lys Lys Val Ser Phe Ala

340 345 350

Arg Leu His Leu Ala Ser Ser Phe Lys Asn Leu Val Ser Leu Gln Glu 355' 360 365

Leu Asn Met Asn Gly Ile Phe Phe Arg Ser Leu Asn Lys Tyr Thr Leu 370 375 380

Arg Trp Leu Ala Asp Leu Pro Lys Leu His Thr Leu His Leu Gln Met 385 390 395 400

Asn Phe Ile Asn Gln Ala Gln Leu Ser Ile Phe Gly Thr Phe Arg Ala 405 410 415

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Leu Leu Ser Ala Asp Pro His Pro Ala Pro Leu Ser Thr Pro Ala Ser 450 455 460

Lys Asn Phe Met Asp Arg Cys Lys Asn Phe Lys Phe Thr Met Asp Leu 465 470 475 480

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Ser Arg Asn Asn Leu Val Thr Ile Lys Pro Glu Met Phe Val Asn Leu 485 490 490

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Ser Arg Leu Gln Cys Leu Ser Leu Ser His Asn Ser Ile Ala Gln Ala 500 505 510

Val Asn Gly Ser Gln Phe Leu Pro Leu Thr Asn Leu Gln Val Leu Asp 515 520 525

Leu Ser His Asn Lys Leu Asp Leu Tyr His Trp Lys Ser Phe Ser Glu 530 535

Leu Pro Gln Leu Gln Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe 545 550 555

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Met Leu His Ser Leu Ser Leu Ala His Asn Asp Ile His Thr Arg Val 580 585 590

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- Phe Gln Gly Leu Ser Gly Leu Leu Lys Leu Asp Leu Ser Gln Asn Asn 625 630 635 640
- Leu His Ile Leu Arg Pro Gln Asn Leu Asp Asn Leu Pro Lys Ser Leu 645 650 655
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- Gln Lys Leu Asp Val Ser Ser Asn Ser Ile Val Ser Val Val Pro Ala 705 720
- PherPhe-Ala-Leu Ala-VallGlu Leu Lys Glu Val Asn Leu Ser His Asn 725 730 735
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Phe Leu Lys Ser Val Pro His Phe Ser Met Ala Ala Pro Arg Gly Asn 55

Val Thr Ser Leu Ser Leu Ser Ser Asn Arg Ile His His Leu His Asp 75

Ser Asp Phe Ala His Leu Pro Ser Leu Arg His Leu Asn Leu Lys Trp 85 90 95

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- Thr Ile Glu Pro Ser Thr Phe Leu Ala Val Pro Thr Leu Glu Glu Leu 115 120 125
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  165 170 175
- Asn Cys Tyr Tyr Lys Asn Pro Cys Arg Gln Ala Leu: Glu: Val Ala Pro
  180 185 190

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- Gly Ala-Leu Leu Gly Leu Gly Asn-Leu Thr: His-Leu Ser Leu Lys Tyr
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- Asn Asn Leu Thr Val Val Pro Arg Asn Leu Pro Ser Ser Leu Glu Tyr 210 215 220
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Ser Arg Asn Lys Leu Asp Leu Tyr His Glu His Ser Phe Thr Glu Leu

535

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Pro Arg Leu Glu Ala Leu Asp Leu Ser Tyr Asn Ser Gln Pro Phe Gly 545 550 555 560

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Asn Cys Pro Pro Val Gly Leu Ser Pro Met His Phe Pro Cys His Met
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Ala Ser Leu Ala Gly Leu His Ala Leu Arg Phe Leu Phe Met Asp Gly 165 170 175

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- Pro Gln Leu His Pro Asp Thr Phe Ser His Leu Ser Arg Leu Glu Gly 275 280 285
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- Arg Pro Leu Ala Arg Leu Pro Met Leu Gln Thr Leu Arg Leu Gln Met 385 390 395 400
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Leu His Phe Leu Pro Lys Leu Glu Val Leu Asp Leu Ala Gly Asn Arg 675 680 685

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न्त्र अवस्थितिकोति। हि

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240

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